

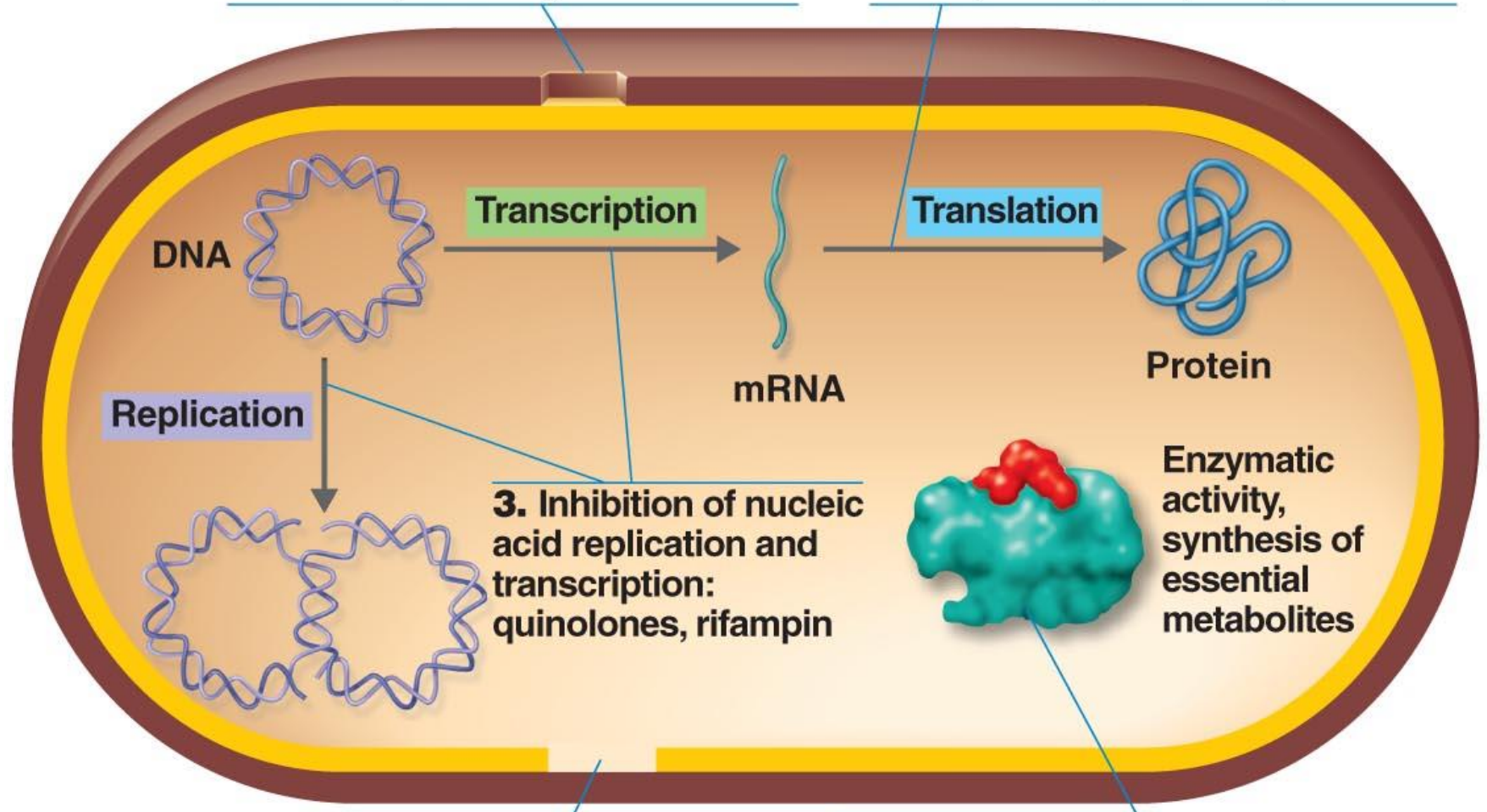
Penicillin



The Action of Antimicrobial Drugs

1. Inhibition of cell wall synthesis:
penicillins, cephalosporins,
bacitracin, vancomycin

2. Inhibition of protein synthesis:
chloramphenicol, erythromycin,
tetracyclines, streptomycin



3. Inhibition of nucleic acid replication and transcription:
quinolones, rifampin

**Enzymatic activity,
synthesis of
essential
metabolites**

4. Injury to plasma membrane:
polymyxin B

**5. Inhibition of synthesis
of essential metabolites:**
sulfanilamide, trimethoprim

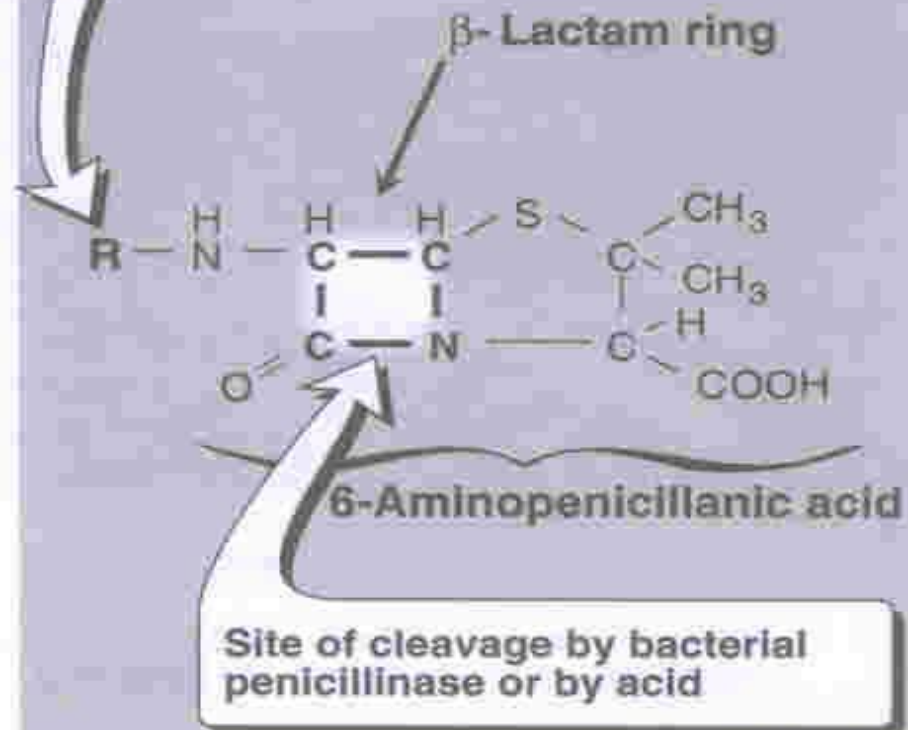
Cell wall Synthesis inhibitors

- Some antimicrobial drugs selectively interfere with the synthesis of bacterial cell wall- a structure that mammalian cell do not possess.
- The cell wall is composed of polymer called peptidoglycan that consists of glycan units joined to each other by peptide cross links.
- To be maximally effective, inhibitors of cell wall synthesis require actively proliferating microorganisms, they have little or no effect on bacteria that are not growing or dividing.
- The most important member of the group are beta lactam antibiotics and vancomycin.

Penicillin

- First antibiotic, extracted from the mould, *Penicillium notatum*. The penicillins are among the most widely effective and least toxic drugs known, but increase resistance has limited their use.
- Member of this family differ from one and another in R substituent attached to the 6-aminopenicillanic acid residue. The nature of this side chain affects the antimicrobial spectrum, stability to stomach acid, cross hypersensitivity and susceptibility to bacterial degradative enzymes (β lactamases).
- Benzylpenicillin (penicillin G) was first natural penicillin available for clinical use. Other natural penicillin are phenoxymethylpenicillin (penicillin V) and phenethicillin.
- All penicillin contain *Penicillin nucleus (6-aminopenicillanic acid)* consisting of a four membered beta lactam ring fused with a thiazolidine ring. The beta lactam rings carries a secondary amino group (R-NH) where acidic radical can be attached to amino group at –R- thereby producing large number of semi synthetic penicillins with different properties.

Nature of the R group determines the drug's stability to enzymatic or acidic hydrolysis, and affects its antibacterial spectrum



Structural features of β -lactam antibiotics.

Members of Penicillin

Penicillin include:

- Amoxicillin
- Ampicillin
- Dicloxacillin
- Indanylcarbencillin
- Nafcillin
- Oxacillin
- Penicillin G
- Penicillin V
- Piperacillin
- Ticarcillin

Classification of Penicillin

1. Narrow Spectrum Penicillin

1. Short acting penicillin (Natural Penicillin)

- Benzylpenicillin
- Phenoxymethyl penicillin
- Phenethicillin

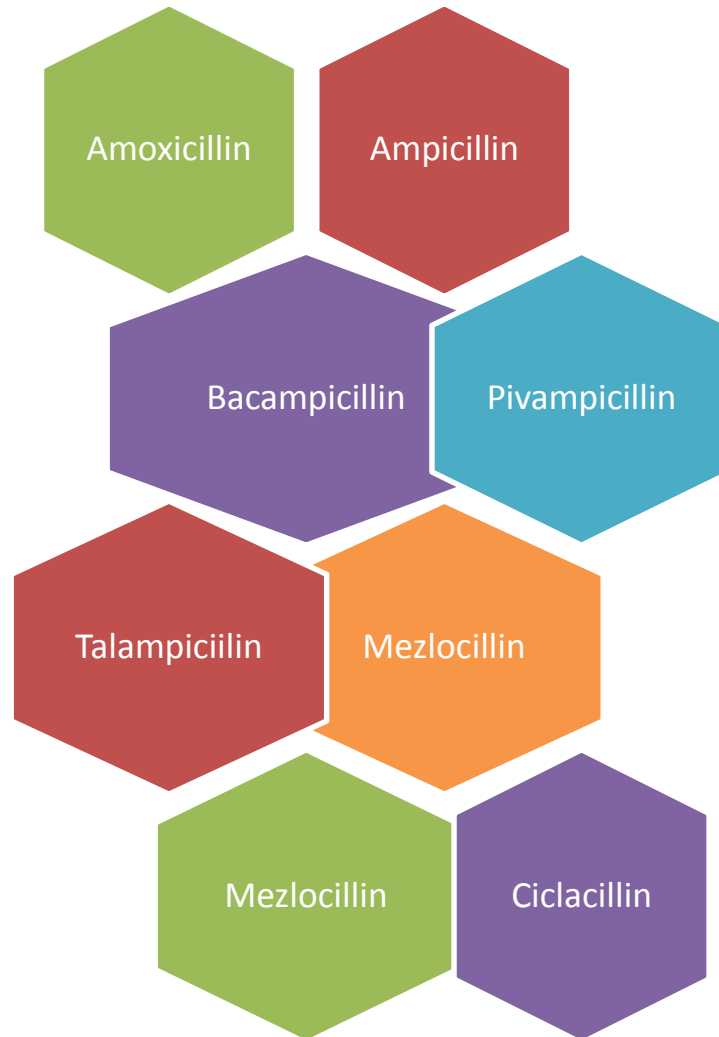
2. Long Acting Penicillin

- Procaine penicillin
- Benethamine penicillin
- Benzathine penicillin

3. Penicillinase Resistant Penicillin

- **AntiStaphylococcal Penicillin**
- - Cloxacillin -
Flucoxacillin –
Methicillin –
Dicloxacillin – Oxacillin
– Nafcillin
- **Penicillin against penicillase producing gram –ive bacteria except pseudomonas**
- -Temocillin

2. Broad Spectrum Penicillin



Broad Spectrum Penicillin Combinations

- Combination of Amoxicillin with Clavulanic Acid
- Combination of Ampicillin with Flucloxacillin
- Combination of Ampicillin with Sulbactam
- Combination of Ticarcillin with Clavulanic acid

3. Anti pseudomonal Penicillin

- Carbenicillin
- Ticarcillin
- Piperacillin

Are antipseudomonal penicillin because of their activity against *P. aeruginosa*.

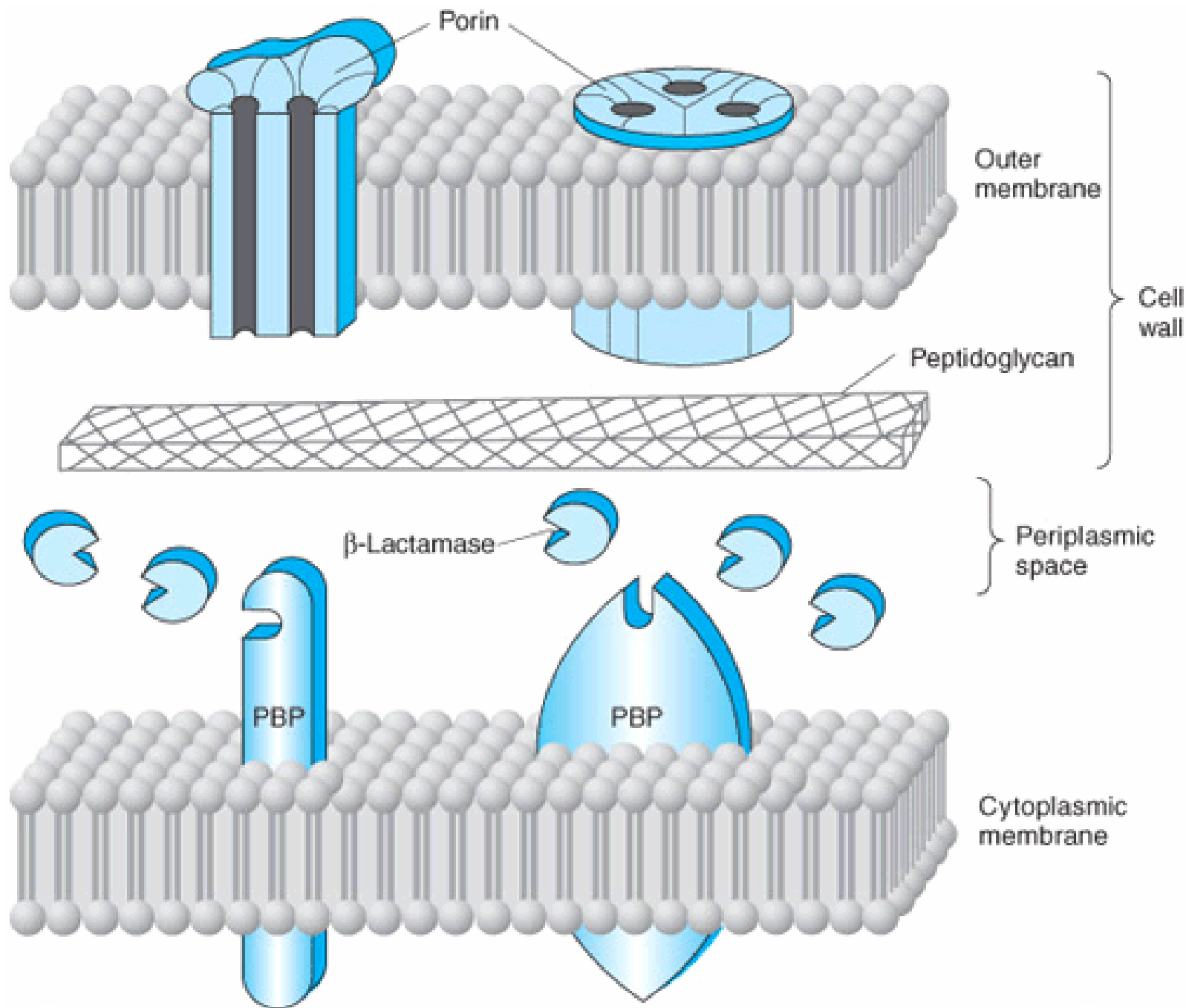
Piperacillin is the most potent of these antibiotics. They are effective against many gram –ive bacilli but not against *klebsiella* because of constitutive penicillinase.

Mechanism of Action of Penicillin

- **Penicillin are bactericidal.** They inhibit the synthesis of bacterial cell wall. They interfere with last step of cell wall synthesis (transpeptidation or cross linkage) resulting in exposure of the osmotically less stable membrane. Cell lysis can occur either through osmotic pressure or through activation of autolysin.
- These drugs are thus bactericidal, the success of penicillin antibiotic in causing cell death is related to **Antibiotic size, charge and hydrophobicity.**
- Penicillin are effective only against rapidly growing microorganisms that synthesize peptidoglycan cell wall. Consequently they are inactive against organisms devoid of this structure such as mycobacteria, protozoa, fungi and viruses.

1. Penicillin Binding Protein

- Penicillin inactivate numerous proteins on the bacteria cell membrane. These **penicillin binding protein (PBPs)** are bacterial enzymes involved in the synthesis of cell wall and in maintenance of morphological features of bacteria
- Exposure of these antibiotics can therefore not only prevent cell wall synthesis but also lead to morphological changes or lysis of susceptible bacteria.
- The number of PBPs varies with type of organisms so alteration in some of target molecules can cause resistance For example Methicillin resistant staphylococcus aureus (MRSA) arose because of this resistant.



2. Inhibition of Transpeptidase

- Some PBPs catalyze formation of cross linkage between peptidoglycan chain. Penicillin inhibit this transpeptidase catalyze reaction, thus hindering the formation of cross links essential for cell wall integrity.

3. Production of Autolysin

- Many bacteria particularly Gram +ive cocci produce degradative enzyme (autolysin) that participate in normal remodeling of bacterial cell wall.
- In the presence of penicillin, degradative action of autolysin proceeds in the absence of cell wall synthesis.

Thus, antibacterial effect of penicillin is result of both inhibition of cell wall synthesis and destruction of existing cell wall by autolysin.

Resistance

- Natural resistance to penicillin occur in organisms that either lack peptidoglycan cell wall for example mycoplasma or have cell walls that are impermeable to drug.

Beta lactamase activity

- This enzyme hydrolyze cyclic amide of β lactam ring which result in loss of bactericidal activity.

Decrease permeability to drug

- Decrease penetration of antibiotic through cell membrane will prevent the drug to reach target PBPS.
- Presence of efflux pump can also reduce amount of intracellular drug.

Altered PBPs

- Modified PBPs have lower affinity for β lactam antibiotics requiring clinically unattainable concentration of drug to effect inhibition of bacterial growth

Pharmacokinetics

Absorption

- Route of administration of a β -lactam antibiotic is determined by the stability of drug to a gastric acid and by severity of infection.
- After oral administration absorption differs greatly for different penicillin.
 - **Not absorbed:** Carbenicillin, ticarcillin
 - **Moderate absorbed:** Benzyl penicillin (penicillin G), ampicillin, Cloxacillin
 - **Well absorbed:** Phenoxymethyl penicillin (Penicillin V), amoxicillin , bacampicillin, Talampicillin, Flucloxacillin, Ciclacillin.

Distribution

- After absorption, penicillin's are widely distributed in body tissue and fluids.
- Entry to CNS is poor.
- This is compensated in treating meningitis by giving large IV oxacillin and Dicloxacillin.

Excretion

- Most of the absorbed penicillin is rapidly excreted by kidneys into urine.
- About 10% of the renal excretion is by glomerular filtration and 90% is by tubular secretion.
- Ampicillin is excreted more slowly than penicillin G.
- Nafcillin is excreted 80% into biliary tract and only 20% by tubular secretion.
- Penicillin is also excreted in sputum and milk.
- Tubular secretion of penicillin can be partially blocked by probenecid.

Dose modification is necessary in several renal failure.

Adverse Effects of Penicillin

- Non toxic And Safe drugs
- Allergic reactions may be severe. Major determinant of penicillin hypersensitivity is penicilloic acid which reacts with protein and serve as hapten to cause immune reaction.

Amoxicillin:

rash 11 hours after
administration



Other (Nonallergic) adverse effects include

- **Diarrhoea** due to alteration in normal intestinal flora
- Sometimes haemolytic, and **thrombocytopenia or interstitial nephritis**.
- Penicillins are presented as their sodium or potassium salts. Physicians should be aware of this unexpected source of sodium or potassium, especially in patients with renal or cardiac disease.
- Neurotoxic: Extremely high plasma penicillin concentrations cause **convulsions**. If injected intrathecally.
- *Decrease coagulation* maybe observe with high doses of piperacillin, ticarcillin and nafcillin.