PENICILLINS

Cell Wall Inhibitors

- Classify beta-lactam antibiotics
- Enlist narrow and broad spectrum Penicillins.
- Enlist anti-pseudomonal, antistaphylococcal/ beta lactamase resistant Penicillin
- Enlist long- and short-acting Penicillins
- Describe anti-bacterial spectrum of Penicillins.
- Describe pharmacokinetics in respect of emphasis on route of administration and excretion of Penicillins
- Describe mechanism of action of Penicillins
- Describe clinical uses of Penecillins
- Describe adverse effects of Penicillins
- Describe contraindications of Penicillins.
- Describe principal mechanism of bacterial resistance to Penicillins
- Describe drug interactions of Penicillins
- Apply formula for interconversion of milligrams and units of Penicillin G.
- Relate pharmacokinetics and pharmacodynamics of Penicillin with their clinical applications / uses.

Classification of cell wall inhibitors

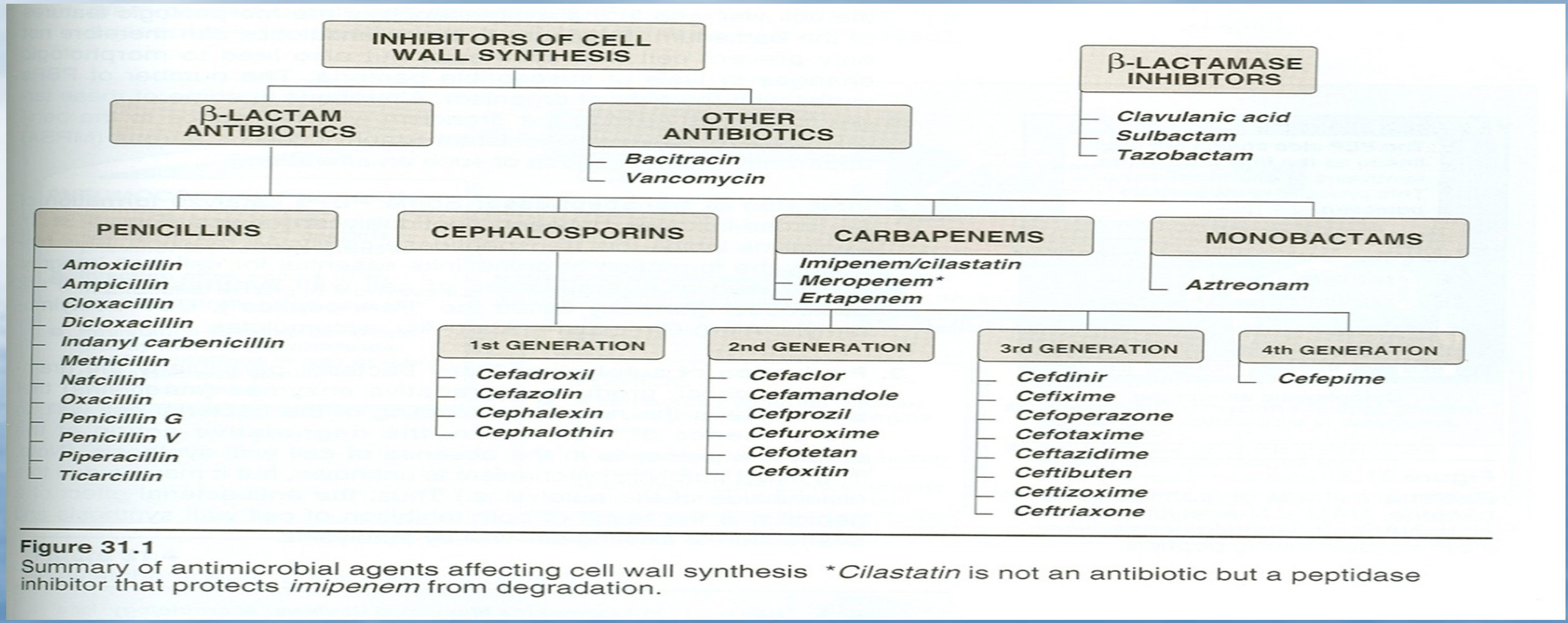


Figure 31.1
Summary of antimicrobial agents affecting cell wall synthesis **Cilastatin* is not an antibiotic but a peptidase inhibitor that protects *imipenem* from degradation.

Classification of penicillins

Narrow spectrum

- Natural penicillins
  - Penicillin G
  - Penicillin V
- Anti-staphylococcal penicillins
  - Methicillin
  - Nafcillin
  - Cloxacillin
  - dicloxacillin

Extended spectrum

- Amoxicillin
- Ampicillin
- Anti pseudomonal
  - carbenicillin
  - piperacillin
  - ticarcillin
  - mezlocillin

β-lactamase resistant penicillins

- methicillin
- nafcillin
- cloxacillin
- oxacillin

β-lactamase inhibitors

- Clavulanic acid
- Sulbactam
- Tazobactam

Long Acting Penicillins

Procaine Penicillin(12-24 hours)

BenethaminePenicillin (2-3days)

Benzyl Penicillin(7-30 days)

Short Acting Penicillins

Penicillin G

Penicillin V

Amoxicillin

Ampicillin

(4-6hours)

Anti bacterial spectrum

Anti-bacterrial spectrum depends upon the

I. Ability of the *penicillins* to pass through the bacterial cell wall to PBP's.

II. The suseptibililty of PBP's to *penicillins* is dependent upon the

a) Size of the molecule of *Penicillins*

b) Charge of the *penicillins*

c) Hydrophobicity of *penicillins.*

Anti bacterial spectrum

Narrow spectrum
penicillin G & penicillin V

- Gram +cocci
- Gram+ive baccilli,
- Gram –ive cocci
- spirochetes.

They not active against penicillinase producing gram + Staphlococci

Very narrow spectrum
Anti Staphylococcal

- Penicillinase producing staphlococci

Anti bacterial spectrum

Extended spectrum
Amoxacillin
Ampicillins

- gram+ive ,
- gram-ive cocci
- and bacilli

H
H-influenza

E
E-coli, E neterococci

L
Listeria monocytogens

P
Proteus

S
Solmonella

Anti bacterial spectrum

Pipericillin

Ticarcillin

Carbenicillin

Pseudomonas Auriginosa

Combination With Beta Lactamase Inhibitors

- Amoxicillin+ Clavulanic Acid
- Ampicillin+ Sulbactam
- Pipericillin+ Tazobactam
- Ticarcillin + Clavulanic Acid

Mechanism of action of Penicillins

The penicillins interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage1),resulting in exposure of the osmotically less stable membrane. Cell lysis can then occur, either through osmotic pressure or through the activation of autolysins

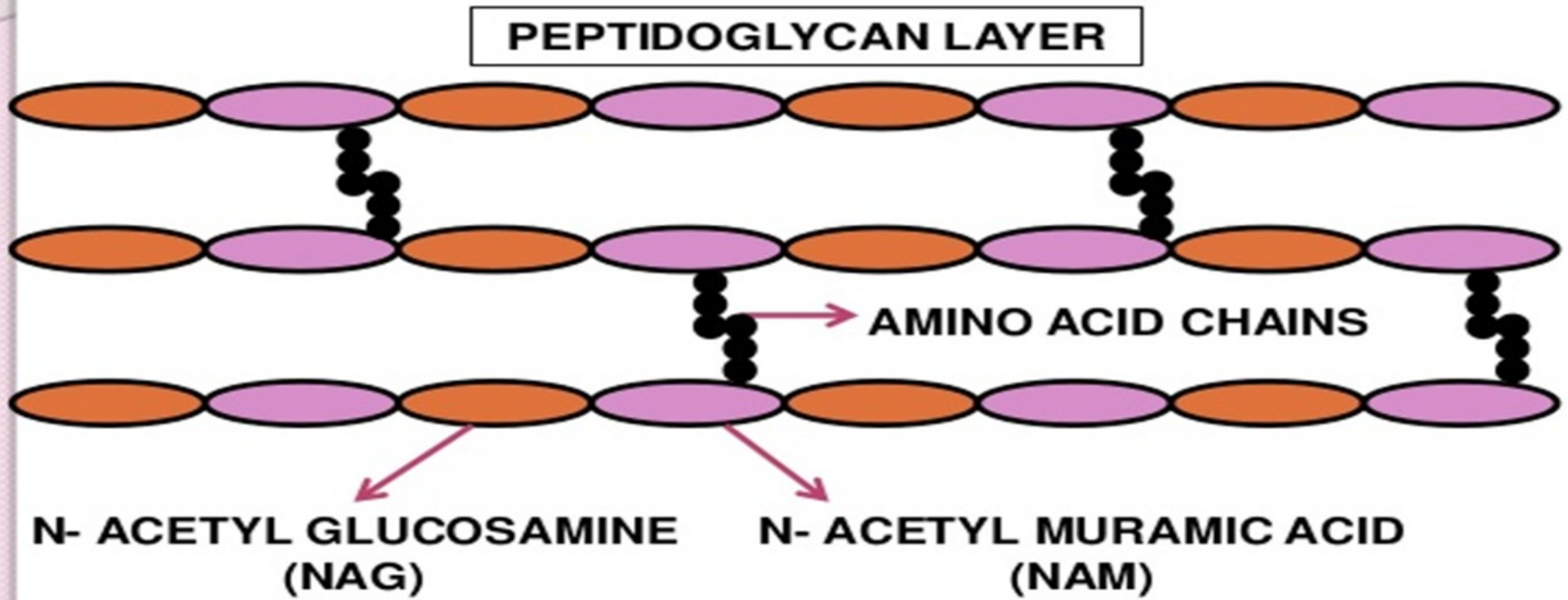
Penicillins are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall.

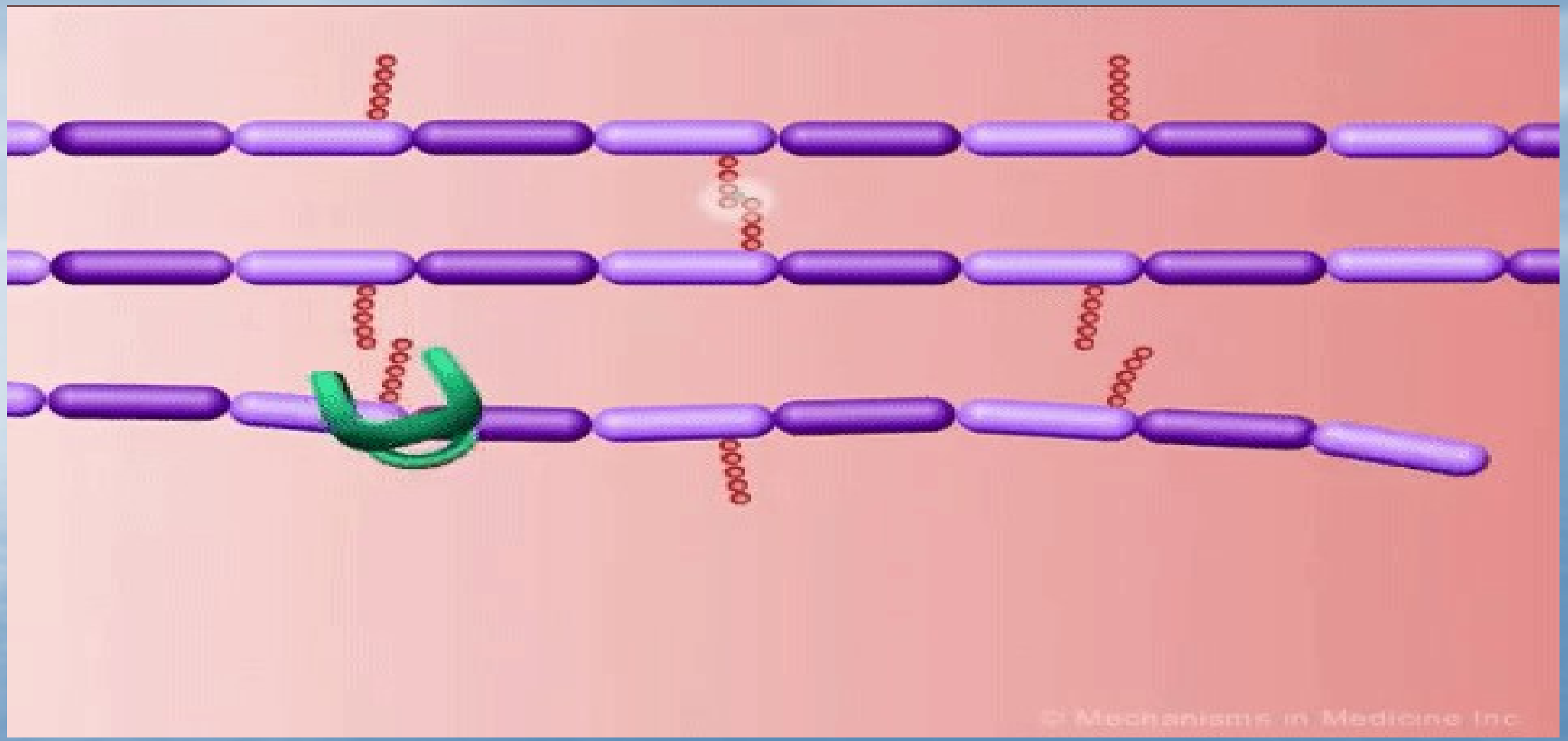
The success of a penicillin antibiotic in causing cell death is related to the antibiotic's size, charge, and hydrophobicity

They are bactericidal drugs

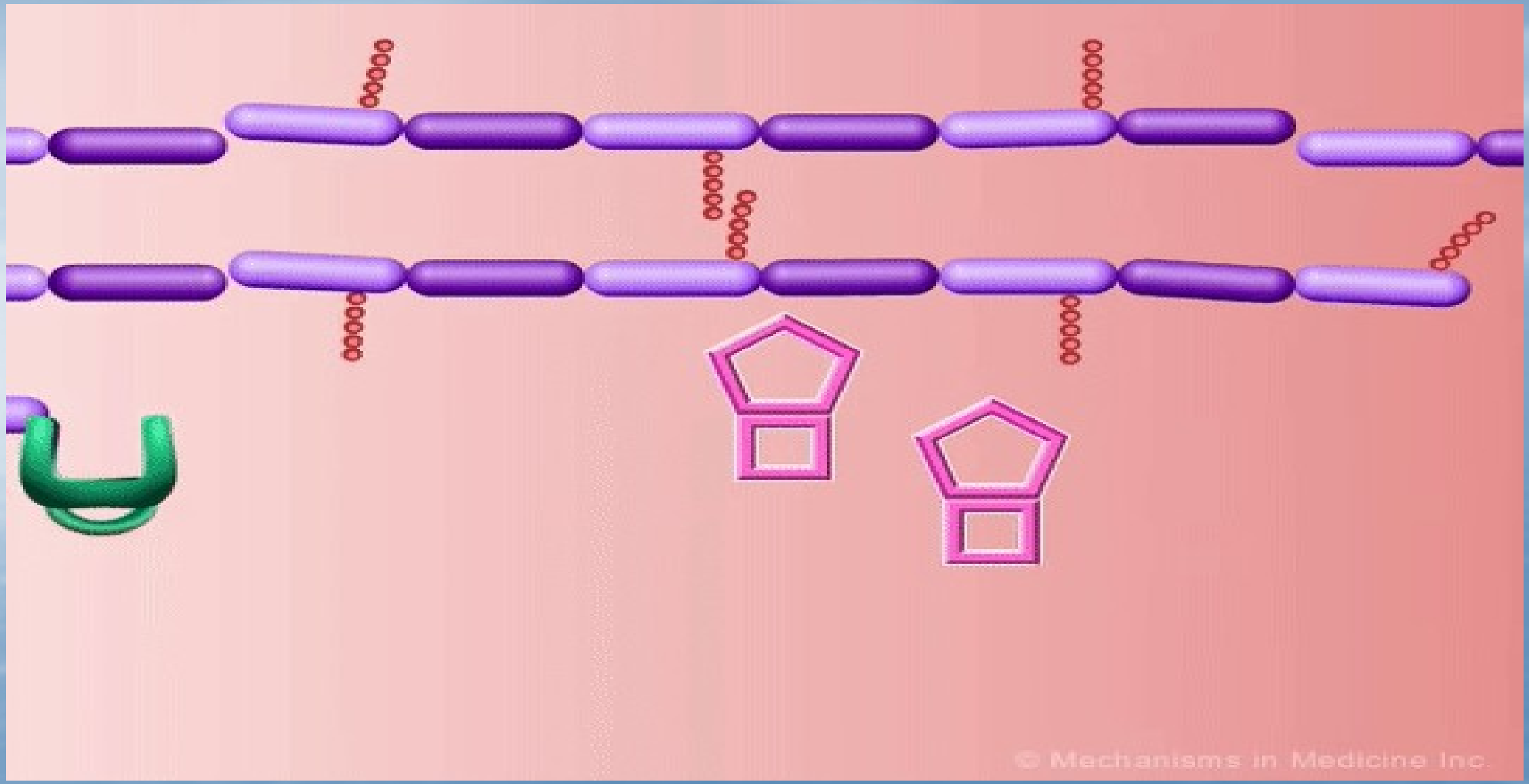
Mechanism of Action

- Interferes with bacterial cell wall synthesis





Normal synthesis of cell by tranpeptidation



MOA of penicillins

Mechanism of action

Penicillin binding proteins: There are a number of proteins on the bacterial cell membrane that are responsible for the synthesis of bacterial cell wall and for the maintenance of morphological features of bacterium.

Penicillin's inactivate these proteins there by disrupting cell wall synthesis as well as morphological features of the bacterium are also affected.

Inhibition of transpeptidase: Some of penicillin binding proteins (PBP) catalyze the cross linkages between peptidoglycan units. These proteins are called Transpeptidases. Penicillin inhibit these transpeptidases as a result of which cross linkages doesn't occur leading to inhibition of bacterial cell wall synthesis.

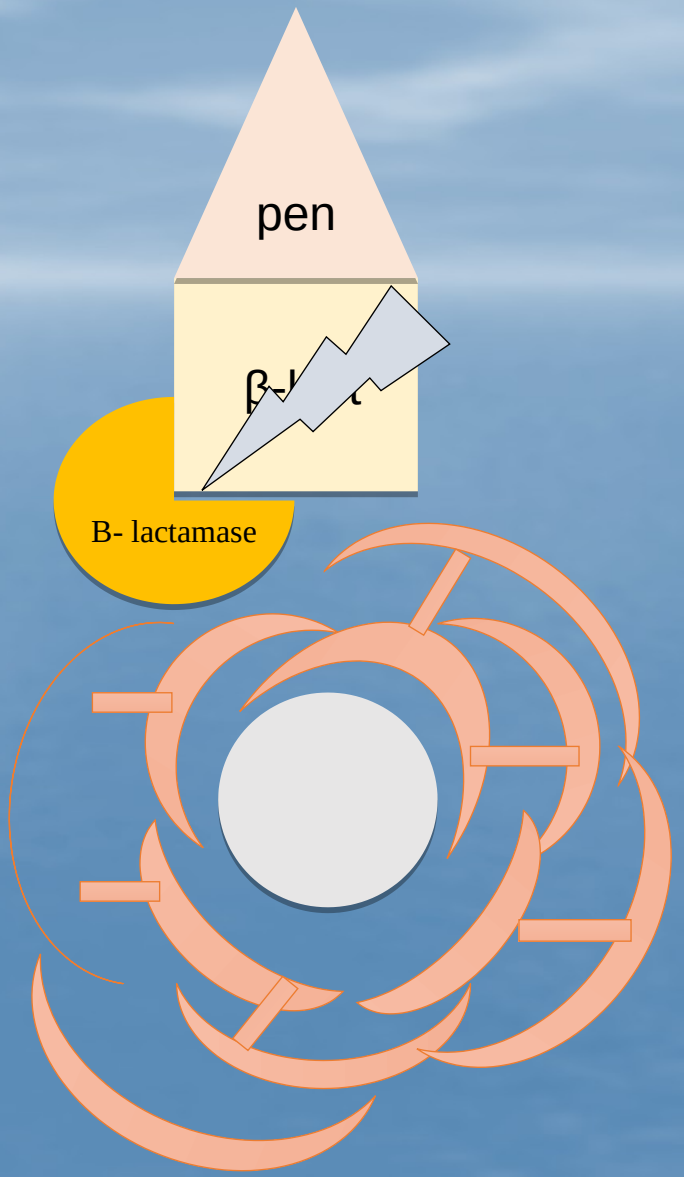
Mechanism of action

Autolysins: for the constant repair and remodeling of bacterial cell walls autolysins are all the time active. The activity of these autolysins in turn is under the control of autolysins inhibitors. Autolysins are all the time under the control of autolysins inhibitors. Penicillin's inhibit these inhibitors along with inhibition of the last step in the synthesis of the cell as a result of which the cell wall is eaten up and further synthesis of the cell wall is also stopped.

Mechanism of resistance

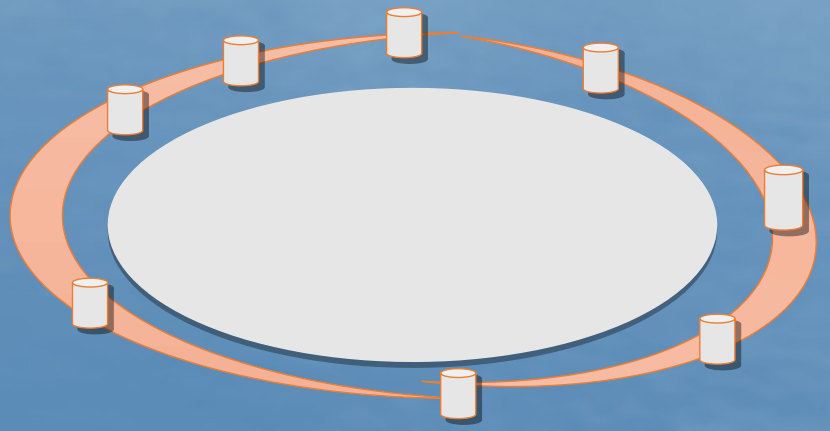
β-lactamase produced by bacteria
Damage the beta lactam ring

Decreased permeability
Due to efflux

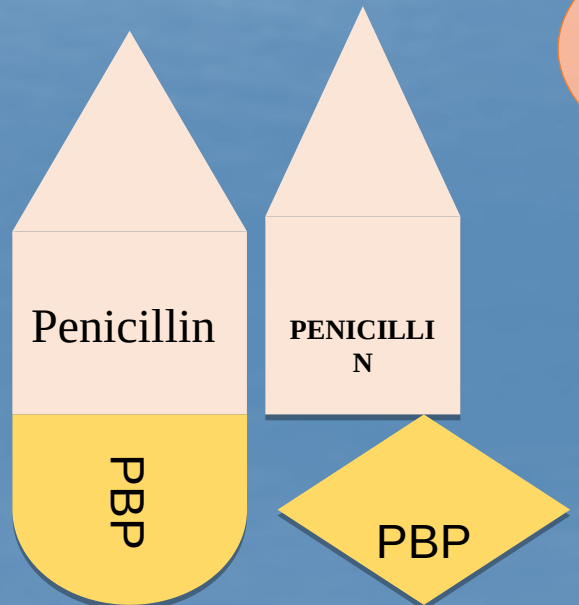


Mechanism of resistance

Decreased permrability due to tightening of porins



Decreased permeability due changes in the Penicillin Binding Proteins



- **Decreased permeability ;**
- Some times there is decreased permeability through the bacterial cell wall, so the penicillins cannot reach the target PBP’s.
- **Efflux pumps:**
- Also some bacteria develop increased number of efflux pumps on the cell membrane so the antibiotics are pushed out.
- **Changes in PBP’s :**
- The PBP’s undergo modifications. The PBP’s loose binding affinity for the penicillins. This results in decreased concentrations of penicillins in the bacteria , not enough to significantly stop bacterial growth.
- For example MRSA there is alteration in the PBP’ therefore than ***Vancomycin*** is then used.

β-lactamase activity:

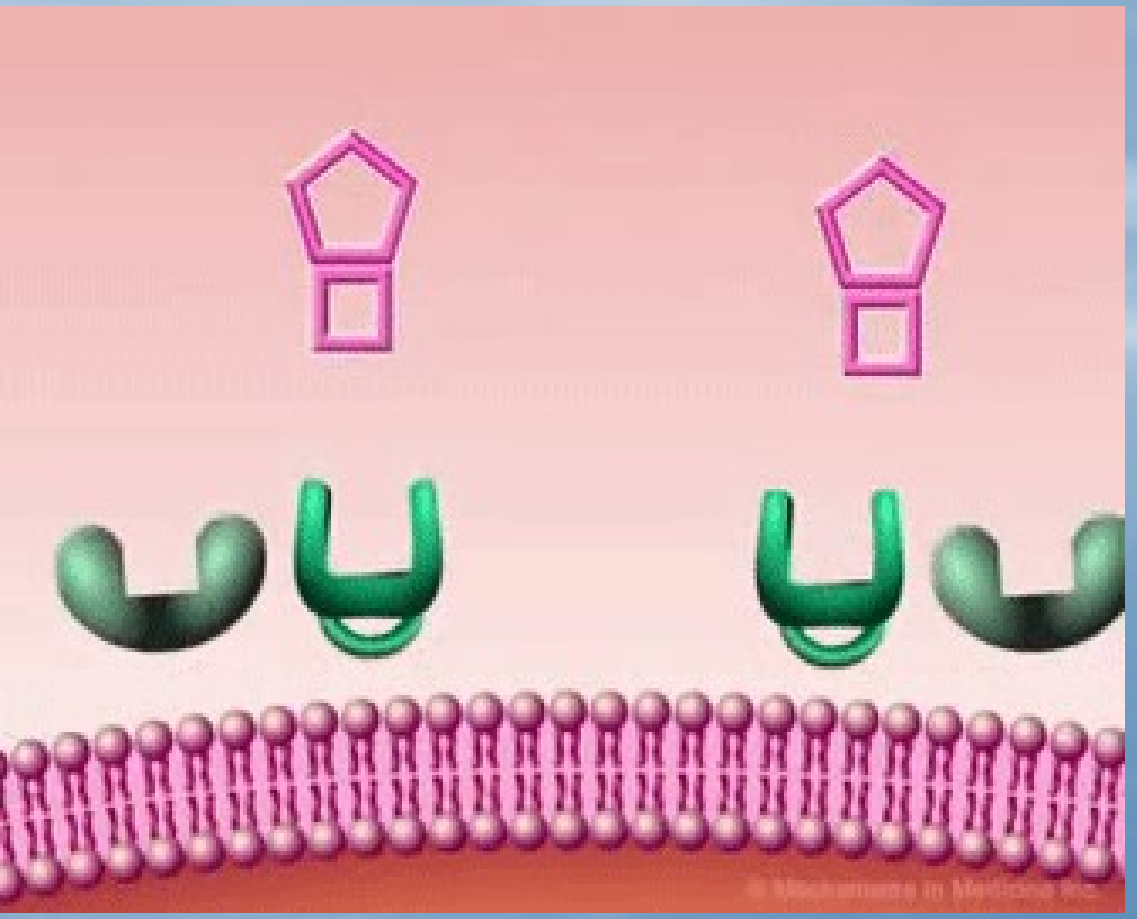
This is the main cause of resistance. They hydrolyse amide bond of β-lactum antibiotics as a result of which they loose their bactericidal activity.

β-lactamase may be constitutional in some bacteria and in some it may be aquired that is plasmid mediated.

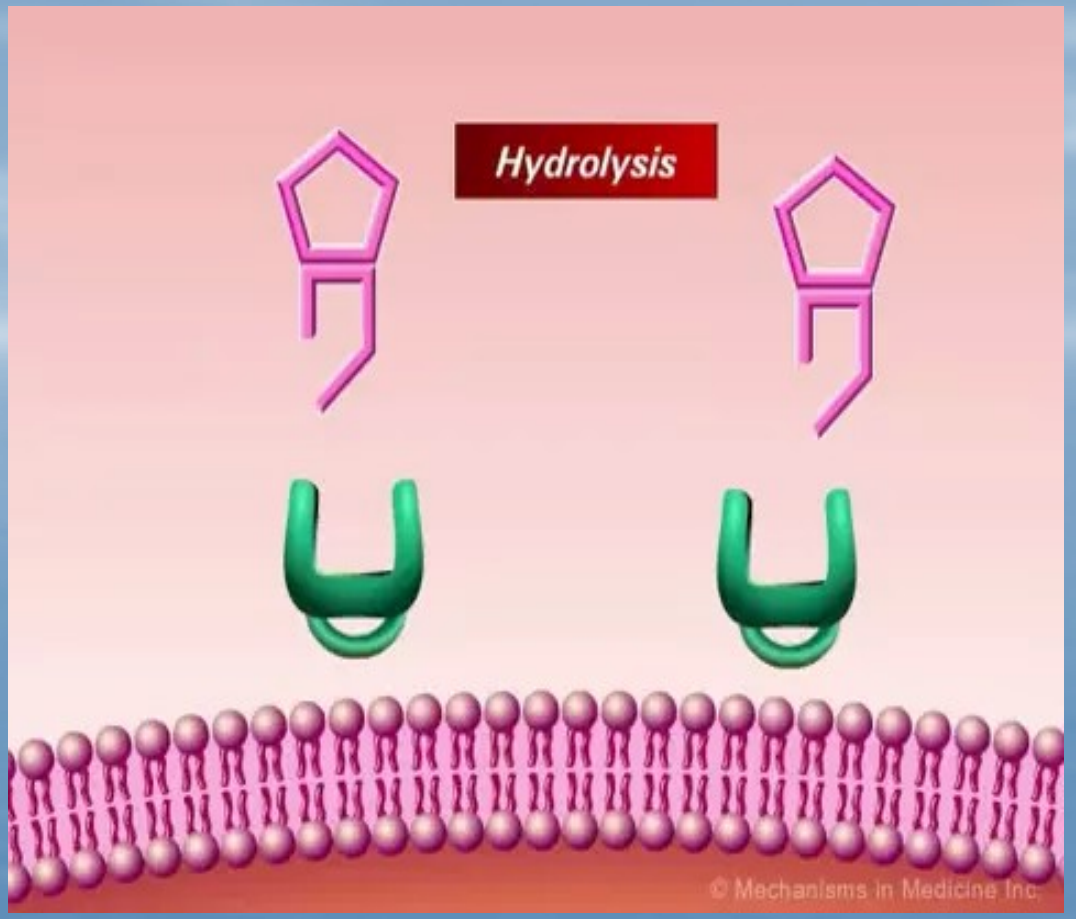
In some it may be chromosomal which is inducible by the β-lactum antibiotics.

On the other hand some of the β-lactum antibiotics are not so vulnerable to β-lactamase and maintain antibacterial activity.

In case of Gram +ive bacteria the β-lactamases go out of the bacterial cells to hydrolyze β-lactum rings of anti-biotics but in case of Gram –ive bacteria the β-lamases are restricted within the periplasmic space. It is because of this that resistance offered by gram-ive is much more stronger.

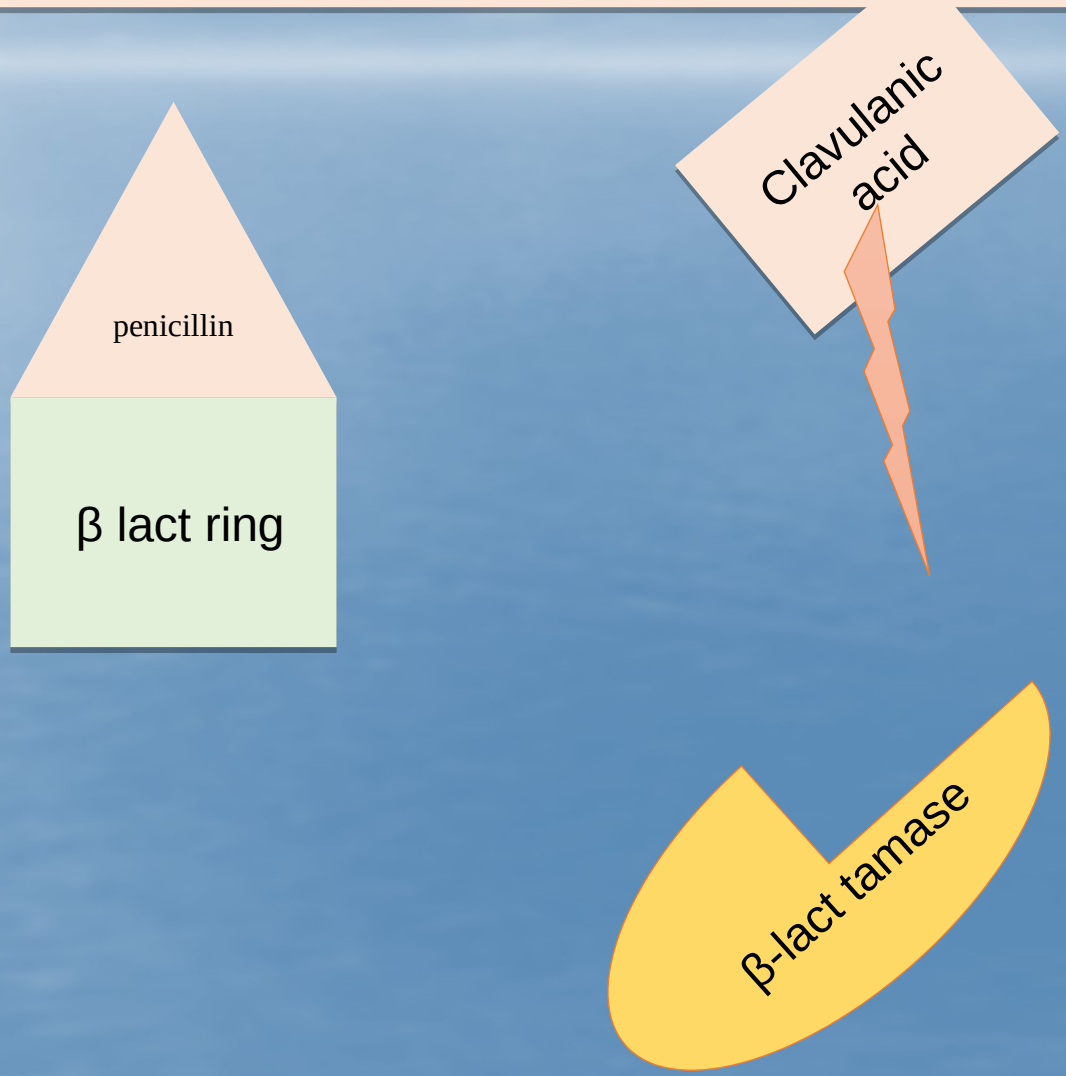


MECHANISM OF BETA LACTAMASES



HYDROLYSIS OF BETA LACTAM RING OF PENICILLINS

Mechanism of action anti-beta lactamases



Pharmacokinetics in respect of emphasis on route of administration and excretion of Penicillins

The route of administration is dependent upon

- Acid stability of the drug.
- Severity of disease.

Acid stable penicillins can be given orally.

Penicillin V
Amoxillin
Ampicillin
.

Acid vulnerable penicillins cannot be given orally.

Penicillin G.

Pharmacokinetics in respect of emphasis on route of administration and excretion of Penicillins

PARENTRALLY

- Penicillin-G,
- Ticarcillin,
- Piperacillin,
- Ticarcillin+clavulanic Acid
- Piperacillin+Tazobctum
- Ampicillin +Sulbactum

Depot forms.
Benzathine Penicillin-G, Procain Penicillin –G are given I/M as depot they are slowly released over a period of time

Excretion

probeniid competes with penicillin G at the site of secretion in the PCV

Penicillin G
The primary route of excretion is through the organic acid (tubular) secretory system of the kidney as well as by glomerular filtration

Nafcillin is eliminated primarily through the biliary route

The penicillins are also excreted into breast milk.

Absorption

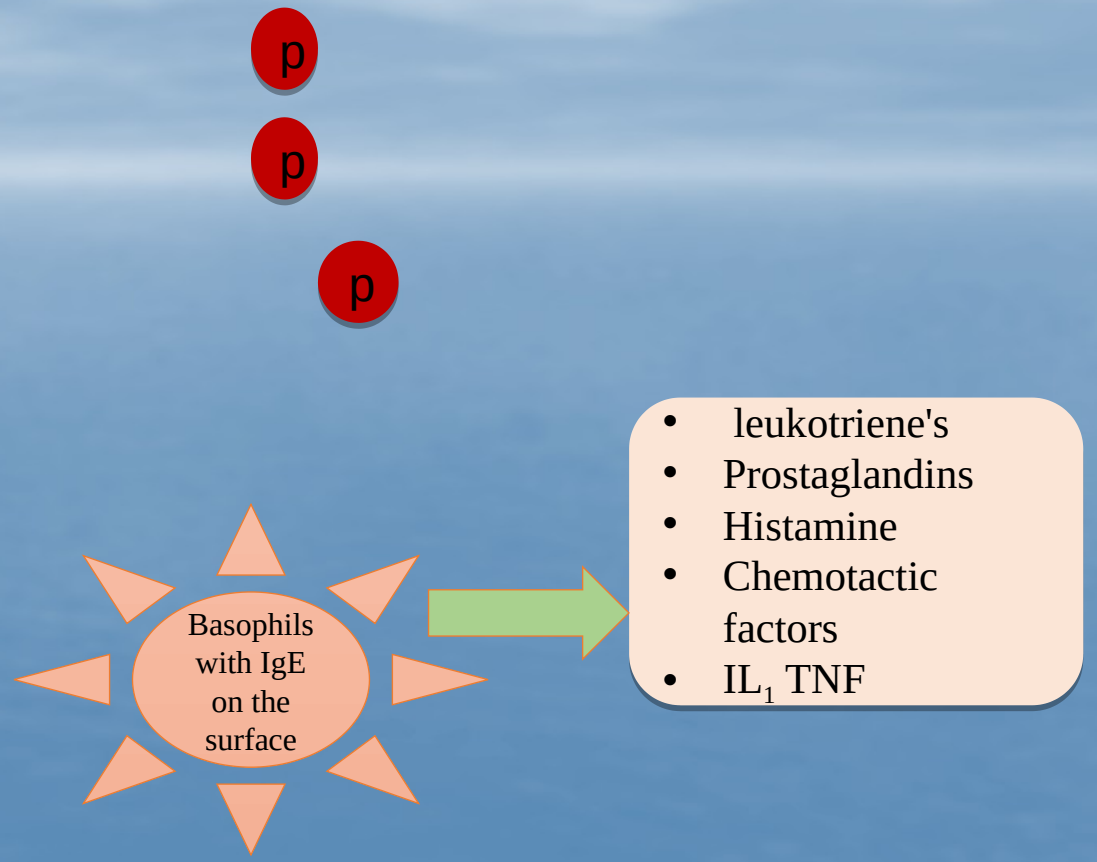
- *Amoxicillin* is almost completely absorbed. Consequently, *it is not appropriate therapy for the* treatment of shigella- or salmonella-derived enteritis, because therapeutically effective levels do not reach the organisms in the intestinal crypts.
- Absorption of all the penicillinase-resistant penicillins is decreased by food in the stomach, because gastric emptying time is lengthened, and the drugs are destroyed in the acidic environment. Therefore, they must be administered 30 to 60 minutes before meals or 2 to 3 hours postprandially. Other penicillins are less affected by food
-

DISTRIBUTION

- The β-lactam antibiotics distribute well throughout the body.
- All the penicillins cross the placental barrier, but none has been shown to be teratogenic.
- Penetration into bone or cerebrospinal fluid (CSF), is insufficient for therapy unless these sites are inflamed, same is the case for bones.
- *Penicillin levels in the prostate are insufficient* to be effective against infections

Adverse Effects

- Mast cells around the BV—Vasodilation– fall of BP
- Mast cell around the skin- rash
- Mast cells around GIT– abdominal pain
- Mast cells around bronchi– bronchoconstriction.
- May even lead to **Anaphylactic shock**.



TYPE1 HYPRERSENTIVITY REACTION(IgE mediated)

Adverse Effects

alters the proteins on surface of RBC'S

Immune System Now Recognize these proteins as foreign bodies and release IgG.

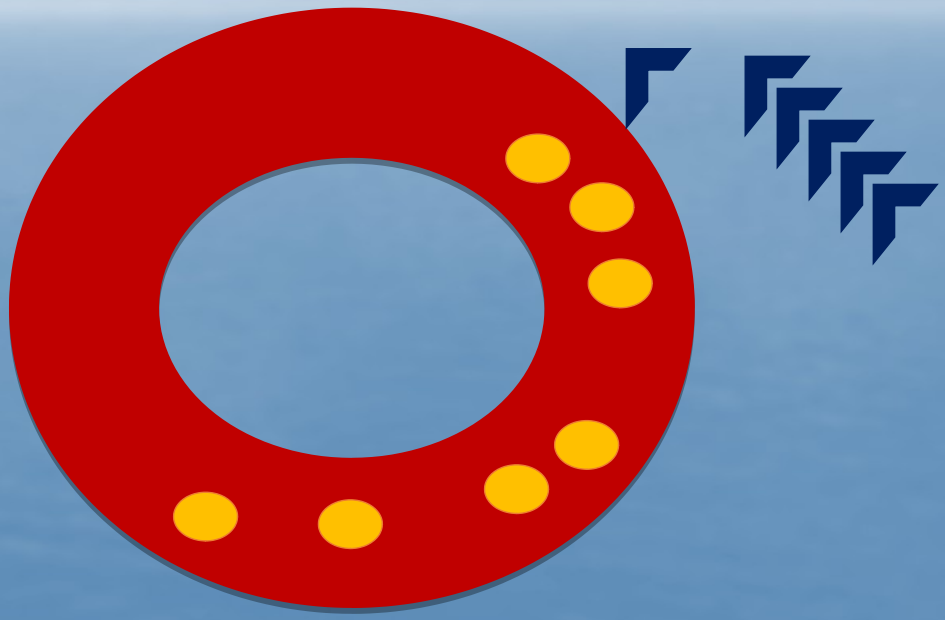
immune system is activated against intrinsic proteins (**antigens**)on the RBC and tissue membrane.
For example when pencillins bind to these antigenic protiens the nature of these proteins is altered.

- PENICILLIN ASSOCIATED **HEMOLYTIC ANEMIA**

TYPE 11 HSR

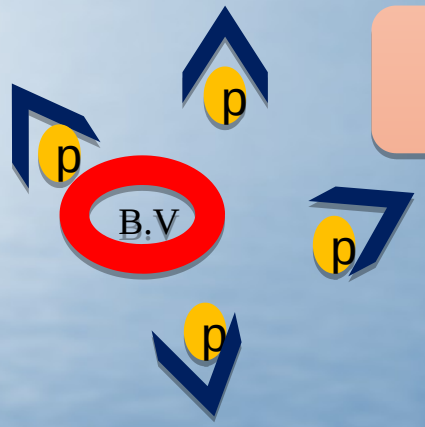
Adverse Effects

penicillin Ag+ IgE/IgG complexes

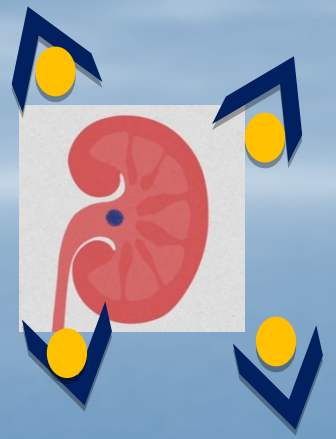


TYPE 111 HSR

Adverse Effects

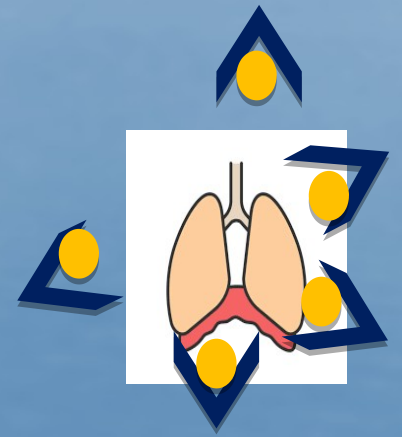


Vasculitis

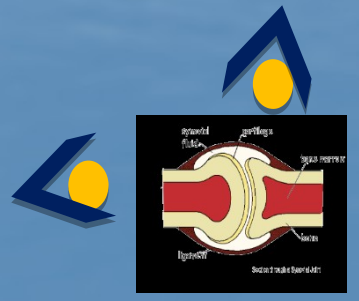


glumerulo-Nephritis

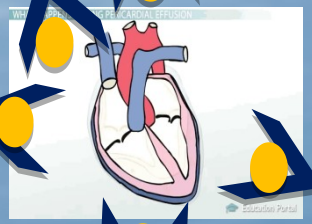
plueristis



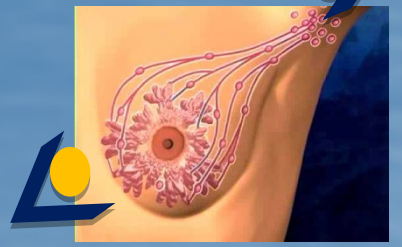
polyarthritis



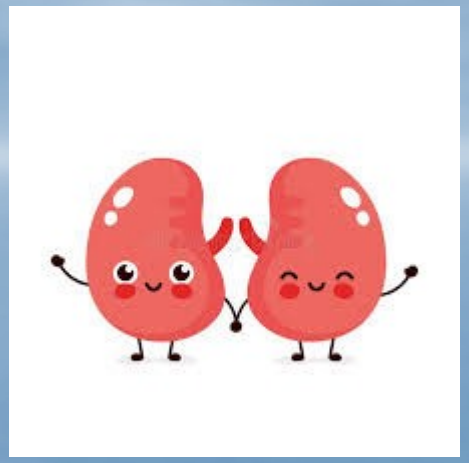
Lymph-adenopathy



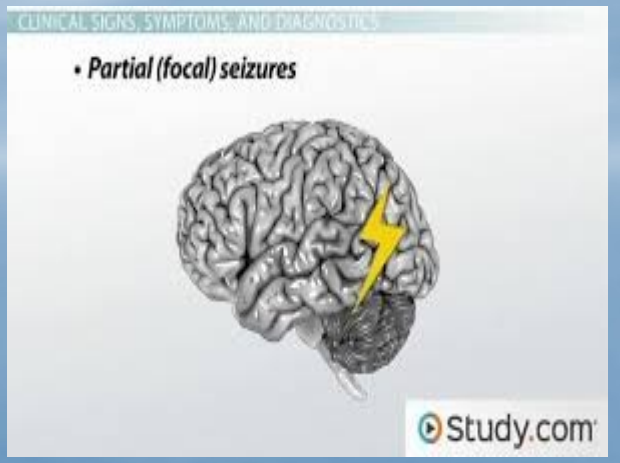
pericarditis



- Diarrhea
- Pseudomembranous colitis



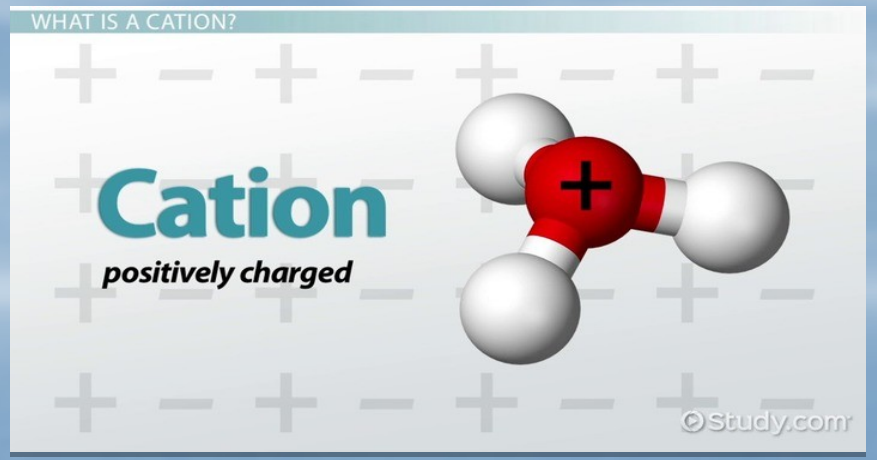
Nephritis : the most notorious among these is ***methicillin***



penicillin and its metabolites reach the CNS they disrupt the cationic channels on the neurons & there is over influx of cations that may precipitate seizures.
So we don’t give penicillin's intra thecally.
Should be monitored in renally compromised patients.

platelets

Carbenicilin, piperacillin and ticarcillin bind with surface receptors on the platlets alter them & reduce their aggregatinting capability.
Neutropenia
Cytopenia specially when used for more than 2 weeks.
Blood complete should be done regularly.



Cation toxicity:
Penicillin's are generally administered as sodium or potassium salts.
Prolonged administration of sodium salt penicillin may lead to water retention along with dilatational hypokalemia. This can be dangerous in cardiac patients

Therapeutic indications

Uses of Penicillin

1. Natural Penicillins

- Streptococcal Infections
- Gram positive rods
- Meningococcal Infections
- Syphilis
- Prophylaxis for scarlet fever

2. Penicillinase-Resistant Penicillins

- Staphylococcal Infections
- Streptococcal infections

3. Aminopenicillins

- Otitis Media
- Bronchitis/Pneumonia
- Enterococcal endocarditis
- Meningitis
- Urinary Tract Infections
- Prophylaxis for bacterial endocarditis
- Lyme Disease and Erlichiosis

4. Broad-Spectrum Penicillins

- Pseudomonas aeruginosa infections
- Mixed infections
- Urinary tract infections & prostatitis
- Surgical prophylaxis

5. B-Lactamase Combinations

a. Amoxicillin + clavulanic acid
- Otitis media, sinusitis, influenza
- Skin and Skin-structure infections

b. Ampicillin + Sulbactam
- Skin & soft tissue infections
- Intra-abdominal infections
- Gynecologic infections

c. Ticarcillin + clavulanic acid
- Septicemia
- Lower respiratory tract infections
- Bone & joint infections
- UTIs

Uses of penicillin:

- Skin and soft tissue infections.
- Diphtheria , tetanus
- Intra abdominal infection
- Ear, lung , infections
- Respiratory tract infection
- Urinary tract infection
- Dental infection
- Syphilis , gonorrhea
- Streptococcol infection

PROPHYLACTIC USES

Rheumatic Fever	***Benzathine Penicillin*** 1.2 MU every 4 weeks till 18 years of age or 5 years after the attach which ever is more.
Bacterial Endocarditis	Dental extractions, Endoscopies or catheterization may lead to bacterial endocarditis specially in those valvular defects.

Drug Interactions Of Penicillins

Drug Interactions

- With Tetracyclines, Chloramphenicol, Erythromycin-
  - Antagonism
- Penicillin with Aminoglycosides-
  - Synergism.
- Penicillin and Aminoglycosides or Penicillin and hydrocortisone in same syringe –
  - Inactivate each other (Pharmaceutical)
- Ampicillin with Allopurinol –
  - High incidence of non-urticarial maculopapular rashes
- Penicillin with Probenecid
  - Prolongs action of penicillin by decreasing tubular secretion