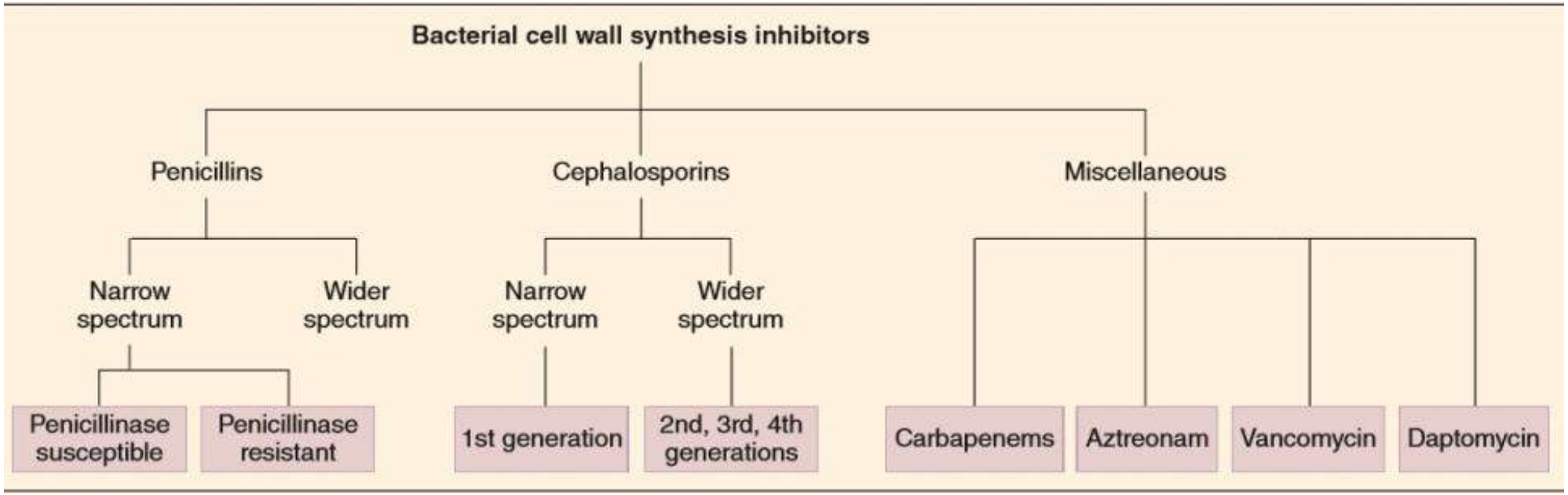
# Cell wall synthesis inhibitors
# Part 1

Pharmacology 3

Dr. Rawan Abudalo

Department of Clinical Pharmacy and Pharmacy Practice
Faculty of Pharmaceutical Sciences
Hashemite University

# Inhibitors of Cell Wall Synthesis

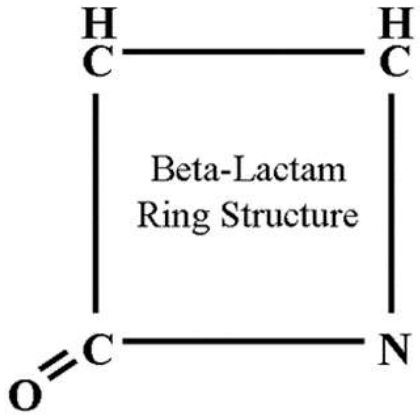


# Inhibition of Cell Wall Synthesis

## β-Lactam Drugs

- The main group of AB that act on bacterial cell wall is the '**beta lactams'; so called due to presence of a β-lactam ring.**
- Irreversibly inhibit enzymes involved in the final steps of cell wall synthesis

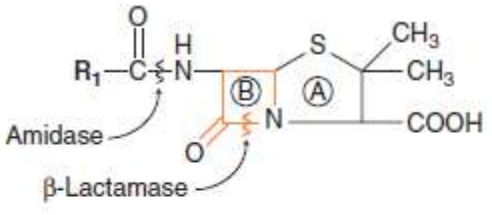
- **β-lactam drugs include:**
  - **Penicillins**
  - **Cephalosporins**
  - **Carbapenems**
  - **Monobactams**



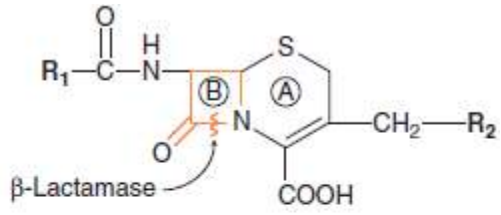
# β-lactam antibiotics

- Basic structures of four groups of β-lactam antibiotics and clavulanic acid.
- The structures illustrate the β-lactam ring (marked B) and the sites of action of bacterial enzymes that inactivate these antibiotics
- (A, thiazolidine ring).

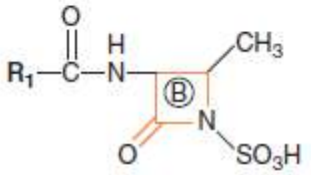
- Bacterial lactamse: Enzyme that hydrolyzes B-Lactam ring and causes loss of activity (acid does that too)



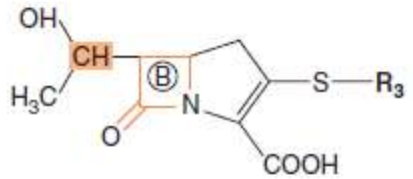

**Penicillin nucleus**



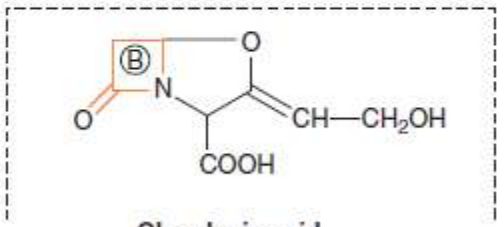

**Cephalosporin nucleus**



**Monobactam nucleus**
(β-lactamase resistant)



**Carbapenem nucleus**
(high resistance to β-lactamases)

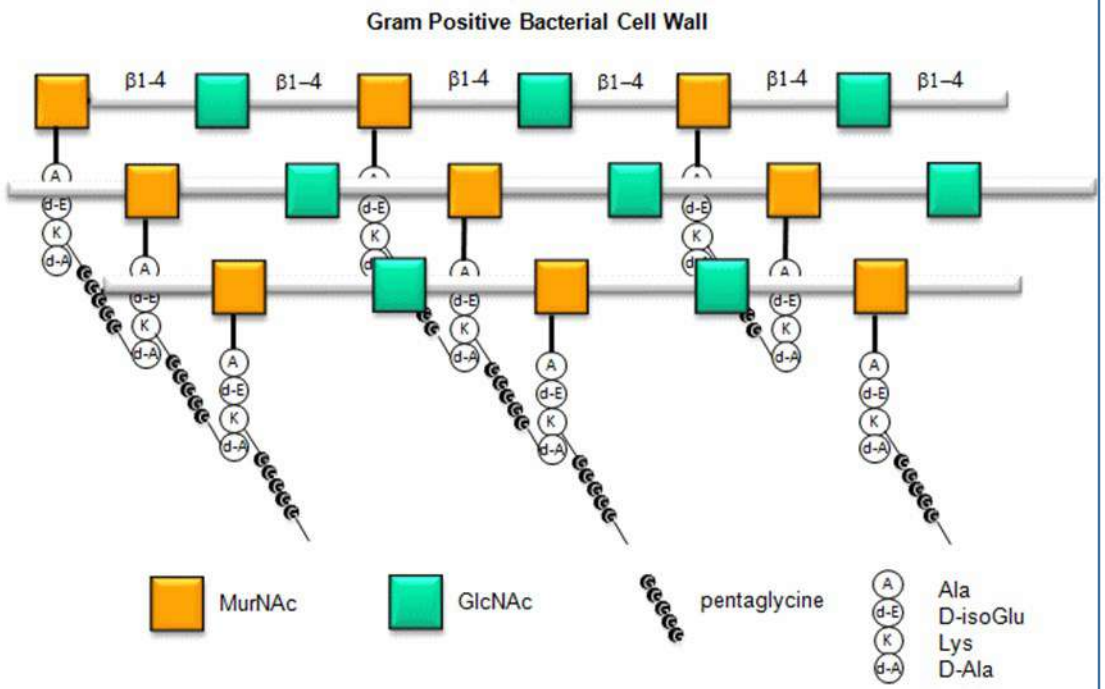


**Clavulanic acid**
(inhibits many β-lactamases)

# Bacterial cell wall

The cell wall is a rigid outer layer that completely surrounds the cytoplasmic membrane, **maintains cell shape and integrity**, and **prevents cell lysis** from high osmotic pressure.

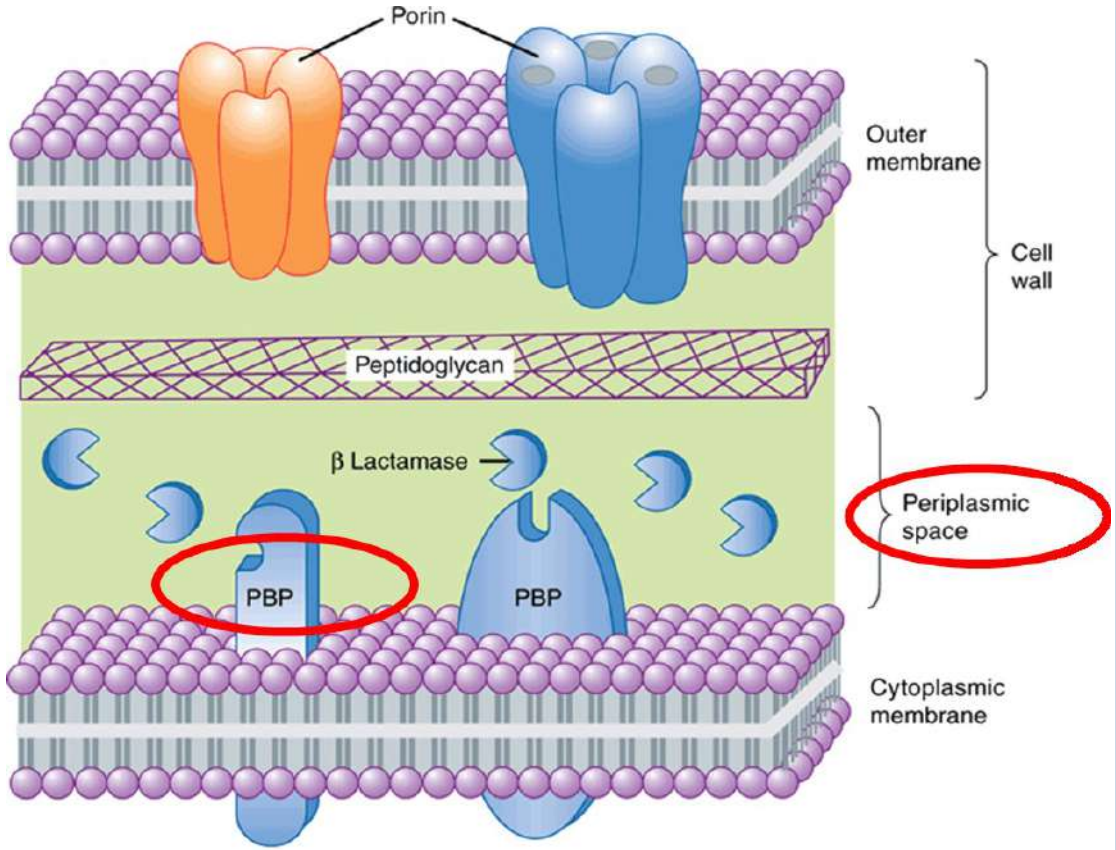
The cell wall is composed of a complex, cross-linked polymer of polysaccharides and polypeptides, **peptidoglycan.**



# Mechanism of action of **β-lactam antibiotics**

- All β-lactam antibiotics interfere with the last step of bacterial cell wall synthesis, which is the cross-linking of adjacent peptidoglycan strands by a process known as **transpeptidation**.

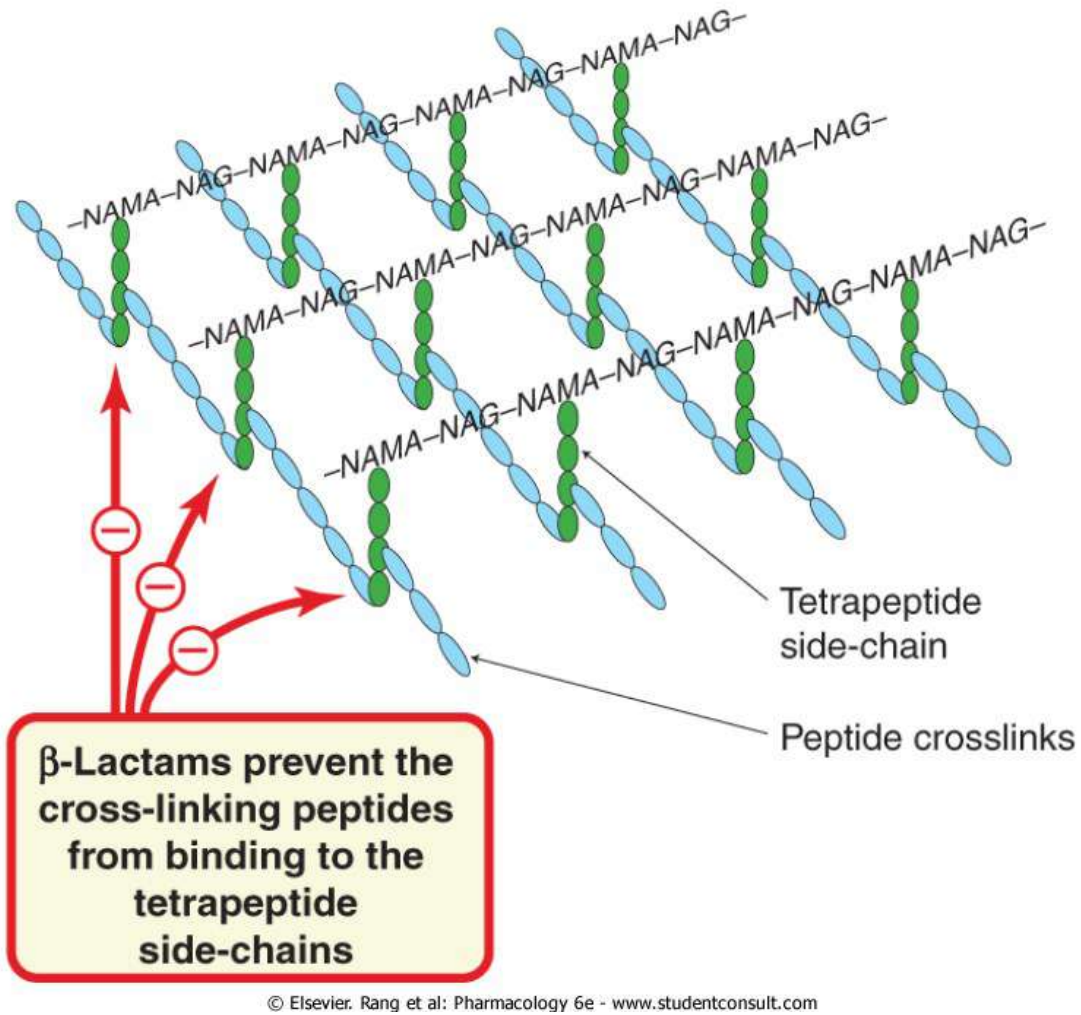
- They compete for and inhibit enzymes called **transpeptidases (Penicillin Binding Proteins (PBP)).**




Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 12th edition*: www.accessmedicine.com

# Mechanism of action of **β-lactam antibiotics**

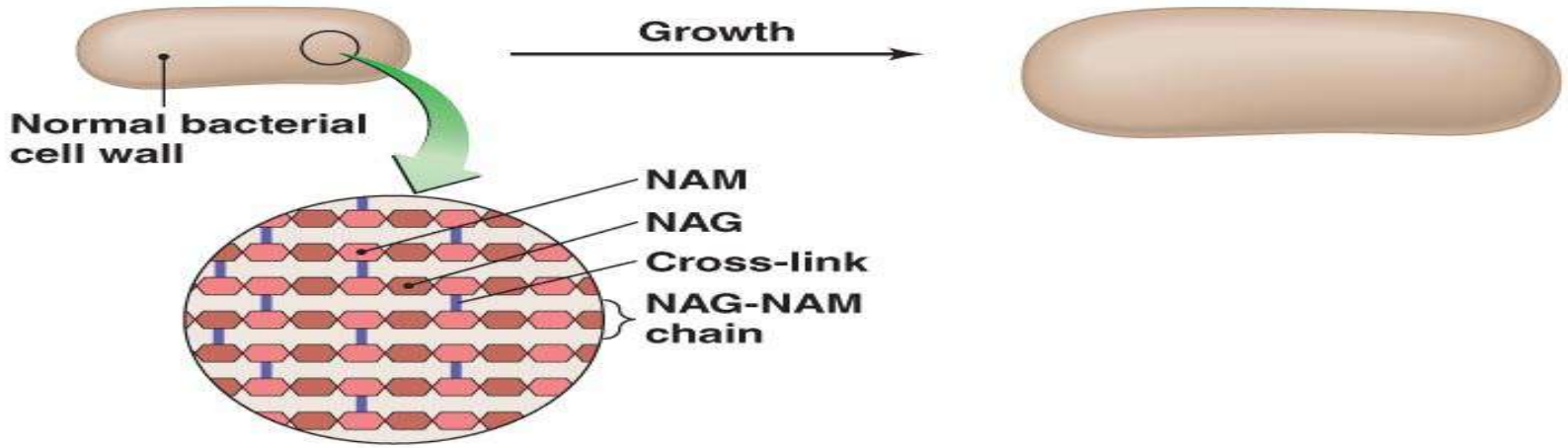
- β-Lactam antibiotics, structural analogs of the natural D-Ala-D-Ala substrate, covalently bind to the active site of PBPs
- They interfere with the last step of bacterial cell wall synthesis (transpeptidation or cross-linkage)
- The result is the formation of a weakened cell wall and ultimately cell death (or this reason, they are regarded as **bactericidal**).



# Mechanism of action of β-lactam antibiotics

A bacterial cell wall is composed of a macromolecule of peptidoglycan composed of NAG-NAM chains that are cross-linked by peptide bridges between the NAM subunits.

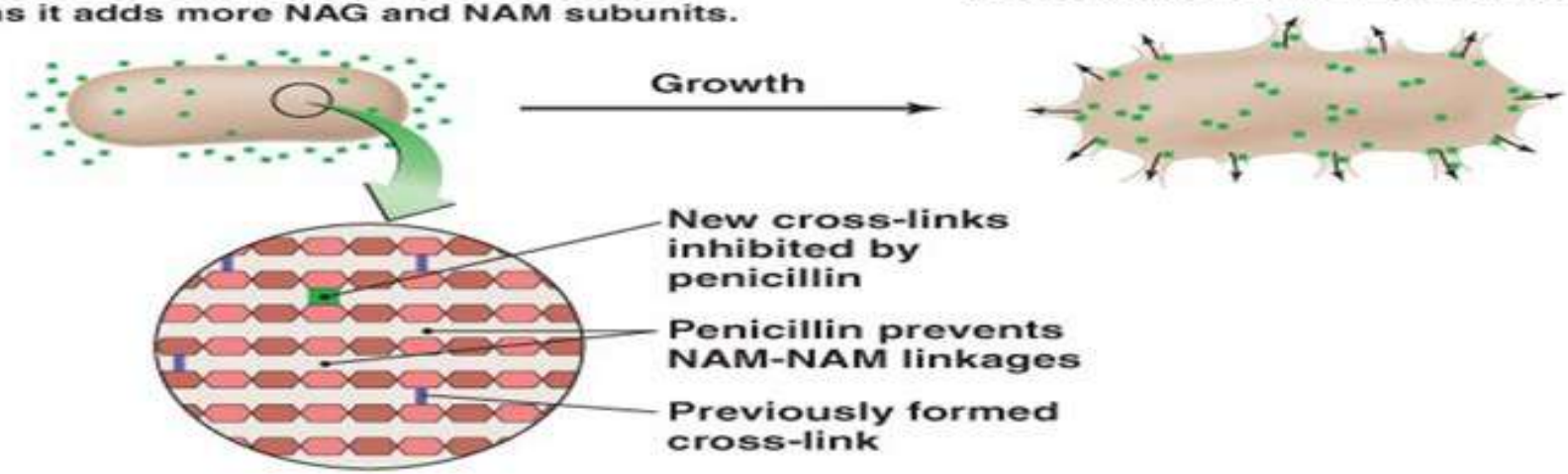
New NAG and NAM subunits are inserted into the wall by enzymes, allowing the cell to grow. Normally, other enzymes link new NAM subunits to old NAM subunits with peptide cross-links.




(a)

Penicillin interferes with the linking enzymes, and NAM subunits remain unattached to their neighbors. However, the cell continues to grow as it adds more NAG and NAM subunits.

The cell bursts from osmotic pressure because the integrity of peptidoglycan is not maintained.




(d)

# History: Discovery & Production

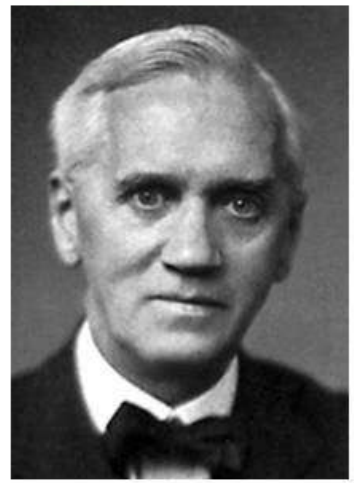
- 1928: Scottish biologist, Alexander Fleming discovered that the *Staphylococcus* culture he had mistakenly left growing in open was contaminated with a mould which had destroyed the bacteria.

A. Fleming

- After isolating a sample and testing it, he found that it belonged to the *Penicillium* family.
  Later the mould was classified as *Penicillium notanum*.

- At first, it was difficult to convince people about its potential uses.

# The Nobel Prize
# Physiology/Medicine 1945



Sir Alexander Fleming
1881 - 1955

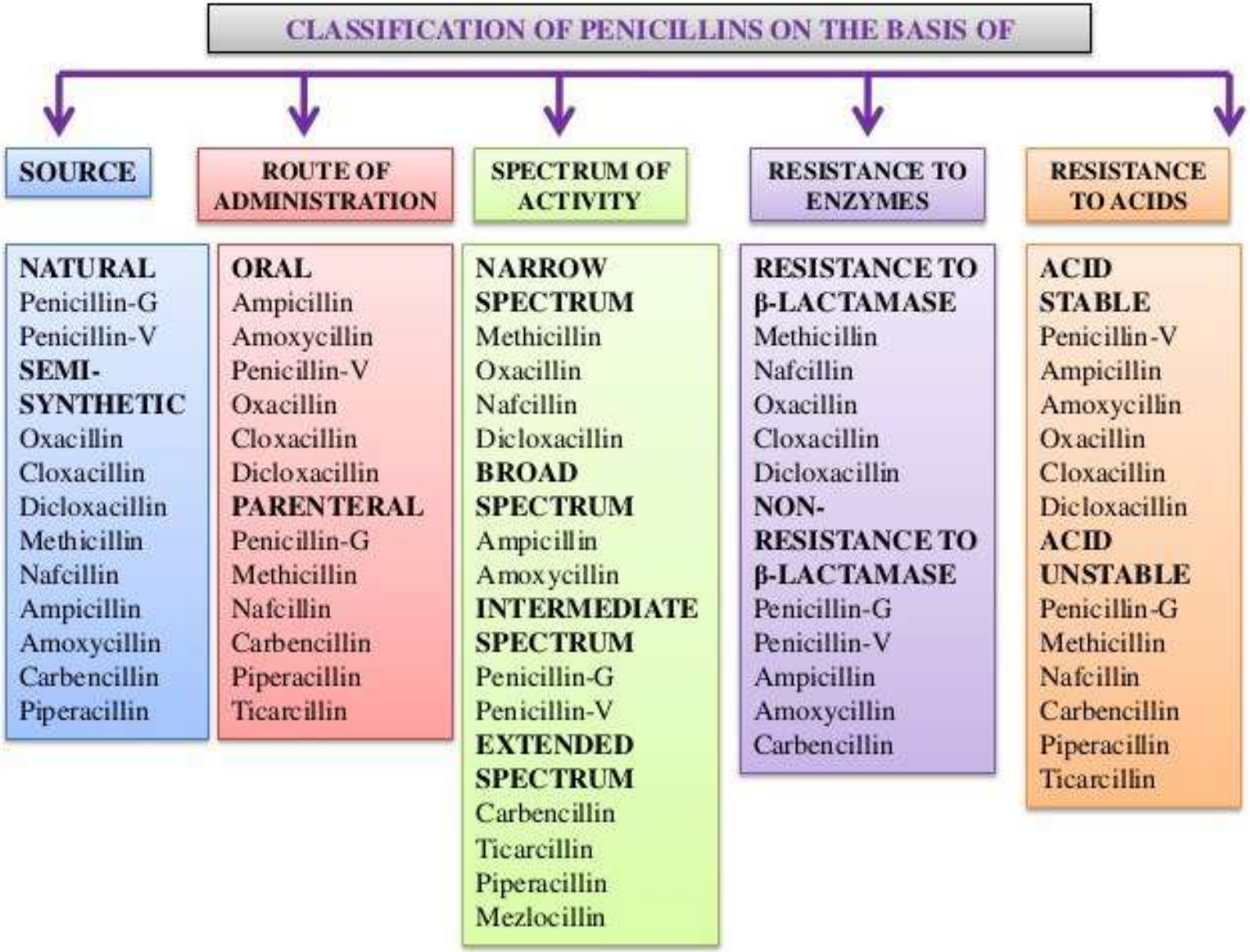
Sir Howard Walter Florey
1898 - 1968

Ernst Boris Chain
1906 - 1979

**Alexander Fleming discovered the antimicrobial properties of penicillin in 1928. Twelve years later, Howard Florey and Ernst Chain developed the processes to produce penicillin in sufficient quantity for it to become widely available**

# Penicillins

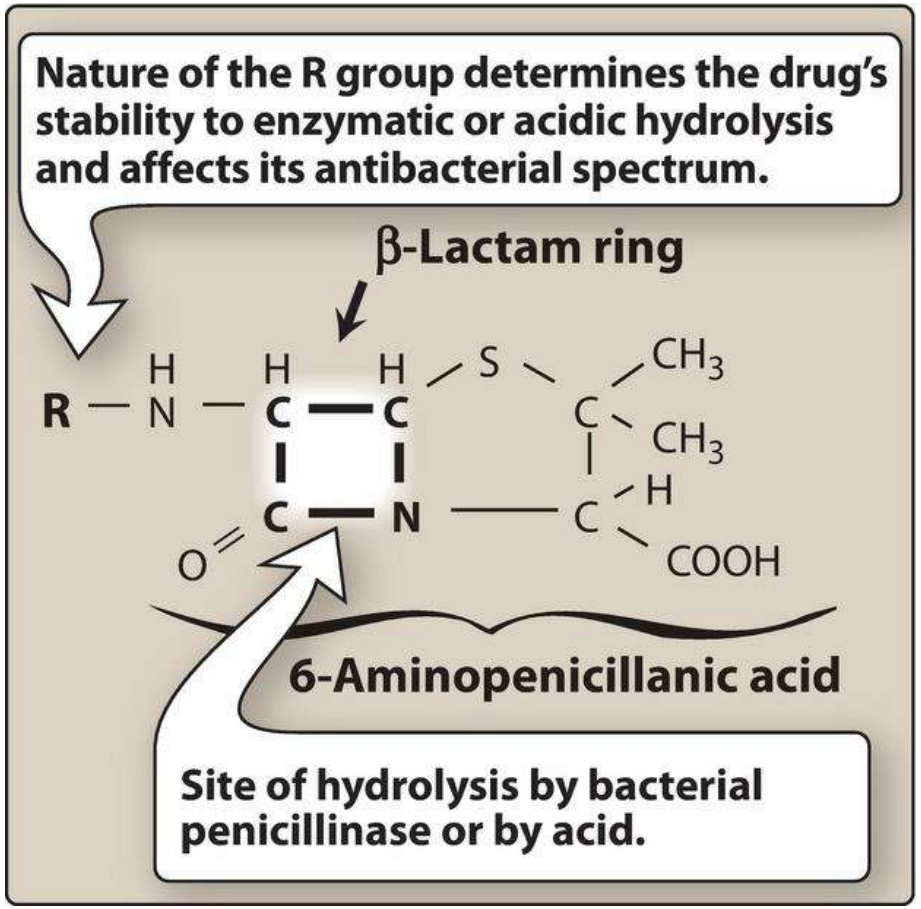
- ✓ The most widely effective and the least toxic drugs known.(interfere with a site or function unique to the growth of m.o)
- ✓ Safe drugs (if we exclude the allergy rxn)
- ✓ Mainly excreted by the kidneys.
- ✓ Suffix : **cillin**


CLASSIFICATION OF PENICILLINS ON THE BASIS OF
SOURCE
NATURAL
Penicillin-G
Penicillin-V
SEMI-SYNTHETIC
Oxacillin
Cloxacillin
Dicloxacillin
Methicillin
Nafcillin
Ampicillin
Amoxycillin
Carbencillin
Piperacillin
ROUTE OF ADMINISTRATION
ORAL
Ampicillin
Amoxycillin
Penicillin-V
Oxacillin
Cloxacillin
Dicloxacillin
PARENTERAL
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin
SPECTRUM OF ACTIVITY
NARROW SPECTRUM
Methicillin
Oxacillin
Nafcillin
Dicloxacillin
BROAD SPECTRUM
Ampicillin
Amoxycillin
INTERMEDIATE SPECTRUM
Penicillin-G
Penicillin-V
EXTENDED SPECTRUM
Carbencillin
Ticarcillin
Piperacillin
Mezlocillin
RESISTANCE TO ENZYMES
RESISTANCE TO β-LACTAMASE
Methicillin
Nafcillin
Oxacillin
Cloxacillin
Dicloxacillin
NON-RESISTANCE TO β-LACTAMASE
Penicillin-G
Penicillin-V
Ampicillin
Amoxycillin
Carbencillin
RESISTANCE TO ACIDS
ACID STABLE
Penicillin-V
Ampicillin
Amoxycillin
Oxacillin
Cloxacillin
Dicloxacillin
ACID UNSTABLE
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin

Chemically penicillins consist of a 6-amino penicillanic acid nucleus with attached side chain (R). Members of penicillin family differ from each other by side chain (R) attached to 6-amino penicillanic acid.

The nature of this side chain affects the:

1. antimicrobial spectrum
2. stability to stomach acid
3. cross-hypersensitivity,
4. susceptibility to bacterial degradative enzymes (β-lactamases).



# Classification of penicillin

## 1- Natural Penicillins

Penicillin G( parenteral)
Penicillin V( oral)

## 2- The extended Spectrum Penicillins

Aminopenicillins :
- Ampicillin
- Amoxicillin

## 3- Anti-pseudomonal Penicillins

Piperacillin

## 4- Penicillinase Resistant Penicillins (anti-staphylococcal)

Cloxacillin.

# 1. Natural Penicillins

- They are  susceptible to inactivation by B-lactamases (penicillinases)
- Narrow -spectrum

## (Benzylpenicillin)
## Penicillin G

-also called Crystalline penicillin.

-it is powder form.

-can be given IV (bolus or infusion) or IM.

- Has short duration (1-2 h).

Destroyed by gastric juice if it is given orally so, **NOT** given orally.

- It is indicated in the treatment of:
  - Syphilis.
  - acute Tonsillitis.
  - tetanus

## (Phenoxymethylpenicillin)
## Penicilin V

- Penicillin V is more acid-stable than penicillin G.
- Given orally (every 4h).
- Oral penicillin .
- It is indicated in the treatment of:

**Tonsillitis.**

Pharyngitis

# Derivatives of **penicillin G**

Long-acting forms:- insoluble salt of penicillin G thus slow abs with long duration.

**1- Procaine penicillin G** (12 h) .

**2- benzathine penicillin G** (4 weeks) .

- Effective in treatment in syphilis.
- Prophylactic in rheumatic fever patients.

- Both are administered **IM** and serve as depot forms.
- they are **suspension** formulation that is **never given by IV** route.

# 2. Extended-spectrum Penicillins or Aminopenicillin:

## Ampicillin and amoxicillin

They are susceptible to inactivation by B-lactamases (penicillinases)

# Ampicillin

- (IV, Oral) is given every 6h (4x1).
- It is used in Bacillary Dysentery.

1g for 5 days + fluids.

- Indicated in listeriosis.

❖ Diarrhea is common side effect WHY????

# Amoxicillin

Orallly is given every 8h (3x1).

❖ better absorbed orally than ampicillin with less diarrhea.

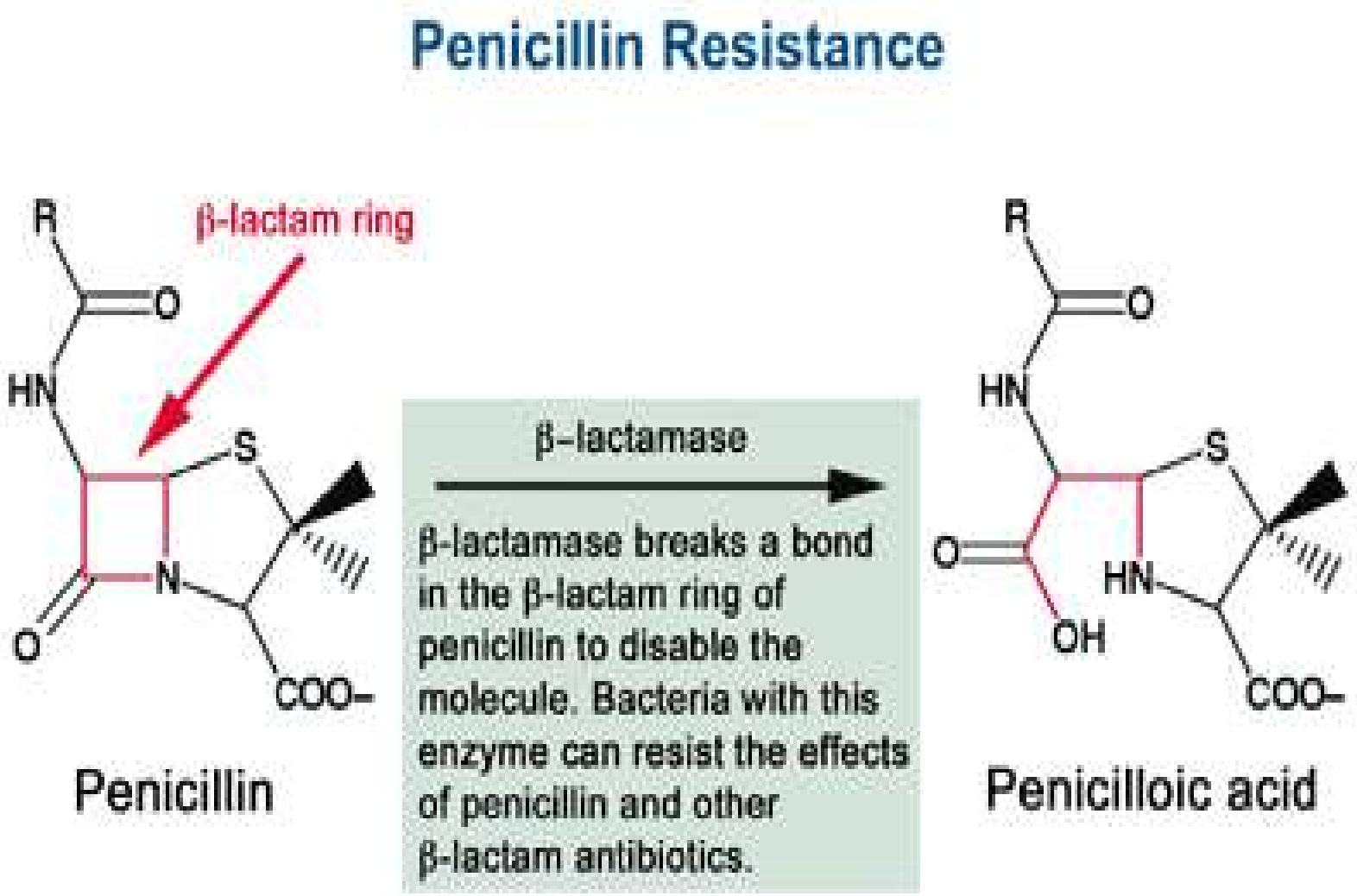
❖ Is employed ***prophylactically by dentists*** for patients with abnormal heart valves who are to undergo extensive oral surgery.

❖ used in treatment of peptic ulcer to eradicates H.Pylori.

❖ Otitis media.

❖ urinary tract infections.

Some bacteria produce β-lactamase enzyme that breaks the critical β-lactam ring



# B-lactamase inhibitors

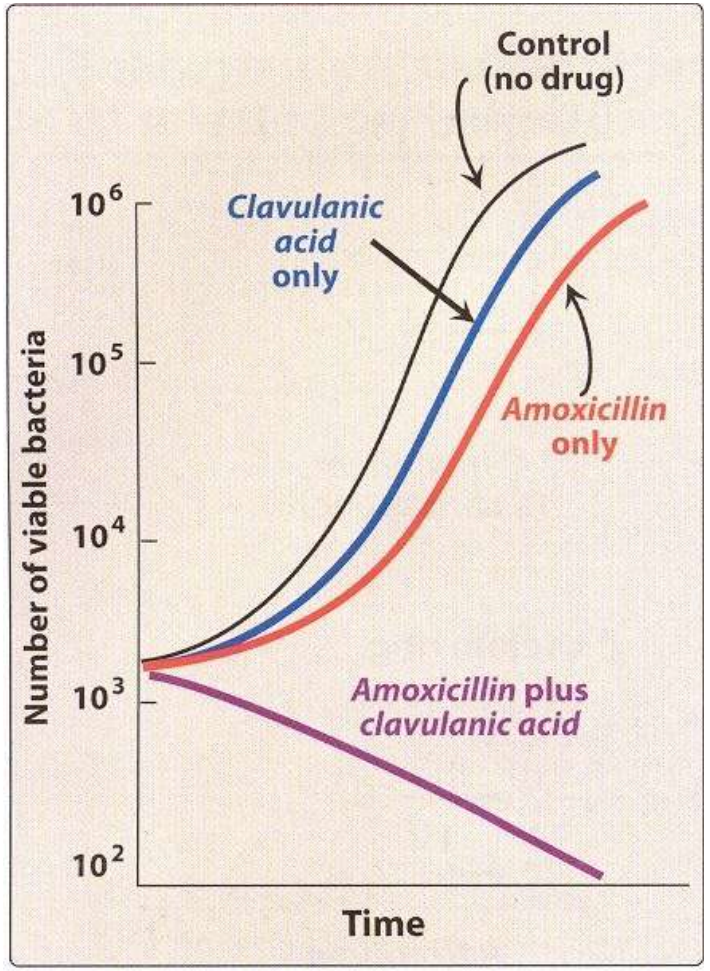
Substance **don't** have antibacterial activity but they have the ability to **inhibit** the B-lactamase enzyme….

Ex. Clavulanic acid

clavulanic acid binds to beta-lactamase and competitively protects amoxicillin

*They potentiating amoxicillin against beta-lactamase producing bacteria.

* It is called "suicide inhibitor"



❑Formulation with a β-lactamase inhibitor, such as :

- *amoxicillin +clavulanic acid*
- *ampicillin +sulbactam*.

❑*protects from*

➢*enzymatic hydrolysis*

➢ *extends their antimicrobial spectra*.

❑without the β-lactamase inhibitor, MSSA is resistant to *ampicillin* and *amoxicillin.*

# 3- Anti staphylococcal penicillins

- Also called anti-staph or penicillinase resistance penicillins.

- **Ex. Methicillin, Flucloxacillin, Cloxacillin, Dicloxacillin, Nafcillin.**
- Given IV & **orally**. (every 4-6 hr)

They are restricted to the treatment of infections caused by penicillinase-producing staphylococci (narrow-spectrum).

- Because of nephrotoxicity caused by **methicillin, nowadays this drug is not** used clinically.
- Strains of staphylcoccus resistant to these drug called : methicillin- resistant staphylococcus aureus (MRSA).
- MRSA is a serious source of nosocomial (hospital-acquired) infections.

(MRSA commonly respond to ***vancomycin.)***

# 4- Anti pseudomonal Penicillins:

- **Ex. Piperacillin, Ticarcillin**

- **Ps.aeruoginosa: G-ve bact** lacks porins → Making these organism resistant to many antimicrobial agents.
- Ps.aeruginose →very difficult to deal with & produce resistance easily.
- Given parentally not orally.

- ***piperacillin with tazobactam***,
- extends the antimicrobial spectrum to include penicillinase-producing organisms.

# Pharmacokinetics of Penicillins

- **Absorption:**
- Penicillins vary in their resistance to gastric acid and therefore vary in their oral bioavailability.

- Examples of compounds relatively stable to gastric acid and suitable for oral administration are penicillin V, dicloxacillin, and amoxicillin.

- Absorption of most oral penicillins (amoxicillin being an exception) is impaired by food (administered at least 1–2 hours before or after a meal).

- **Distribution:**
- Most penicillins cross the blood-brain barrier only when the meninges are inflamed.

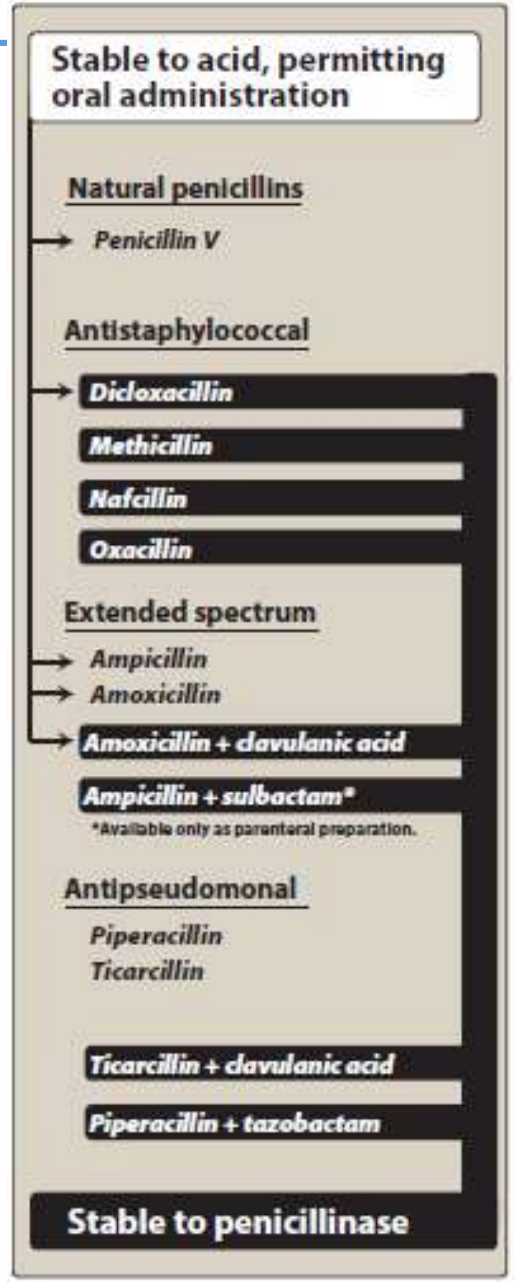
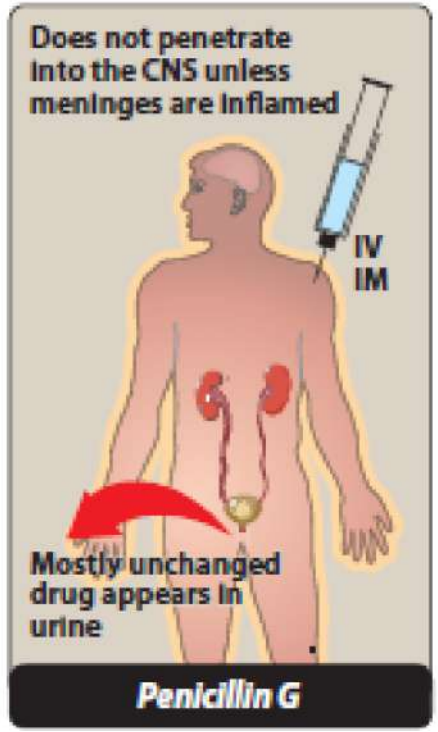



**Figure 38.6**
Stability of the penicillins to acid or the action of penicillinase.

# Pharmacokinetics of Penicillins




- **Metabolism and excretion:**
- Penicillins are polar compounds usually **excreted unchanged in the urine** (inhibited by probenecid).

- Patients with impaired renal function must have dosage regimens adjusted.

- Because nafcillin and oxacillin are primarily metabolized in the liver, they do not require dose adjustment for renal insufficiency.

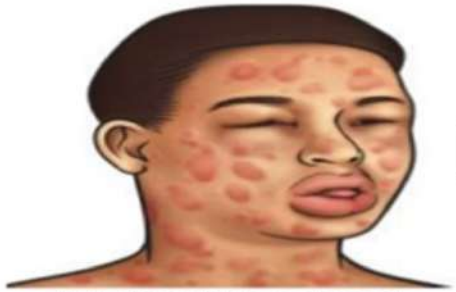
# Adverse reactions of penicillins

## 1-Hypersensitivity reaction :

- 5% of population
- Allergic reactions range from a variety of skin rashes to anaphylactic shock (very rare—0.05% of recipients).

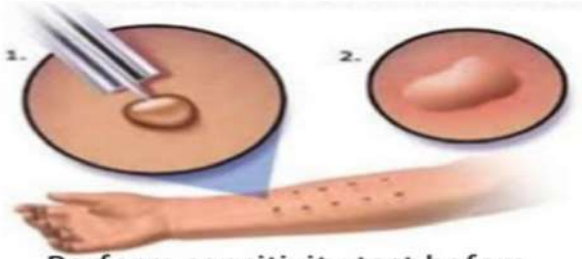
✓ Cross sensitivity with other β-lactam as cephalosporins.

✓ Should be avoided if history is positive



Inj. Penicillin induced anaphylactic shock

To avoid




Perform sensitivity test before administering penicillin Inj.

**2-Diarrhea (most common)**: it is a common problem mainly with (Ampicillin).
**Pseudomembranous colitis** may occur.

3. **Nephritis:** Penicillins, particularly methicillin, have the potential to cause acute interstitial nephritis. [Note: Methicillin is therefore no longer used clinically.]
Piperacillin-tazobactam, when combined with vancomycin, has been associated with greater incidence of acute kidney injury compared to alternate β-lactam agents.

4. **Neurotoxicity:** The penicillins can provoke seizures if injected intrathecally or if very high blood levels are reached.

# Resistance to penicillins and other B-lactams

- Resistance to penicillins and other β-lactams is due to one of four general mechanisms:

1.Inactivation of antibiotic **by B-lactamase (the most common mechanism)**

1.Decreased permeability to the drug

- ➢ is a greater concern in G- (impermeable outer cell wall )

A. Absence or down-regulation of **porins**.

B. Presence of an **efflux pump**, which transport B-lactam antibiotics from the periplasm back across the outer membrane.

3. Modification of **target PBPs**.

- low affinity for binding B-lactam antibiotics
- basis of methicillin resistance in staphylococci (MRSA).

Thank you