بسم الله الرحمن الرحيم

Cell wall inhibitors
Pharmacology of Penicillins

Dr. Mohammad Salem Hareedy

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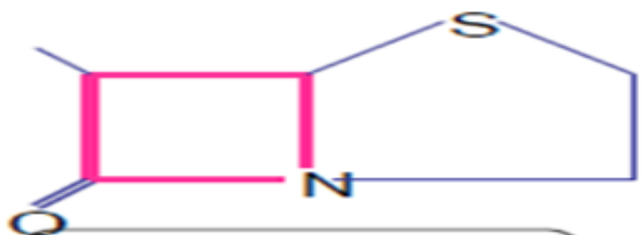
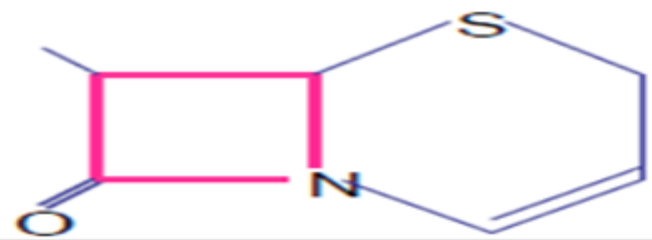
Beta lactam antibacterial drugs

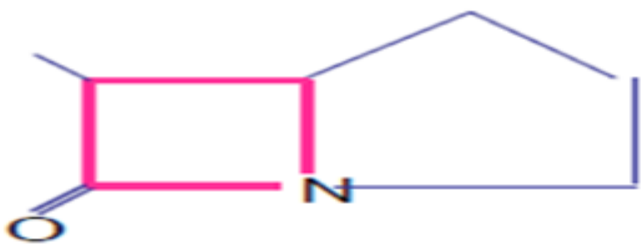
The β-lactams include **penicillins**, **cephalosporins, monobactams** and **carbapenems** and they share a common structure, and a common mechanism of action.



Penicillins



Cephalosporins



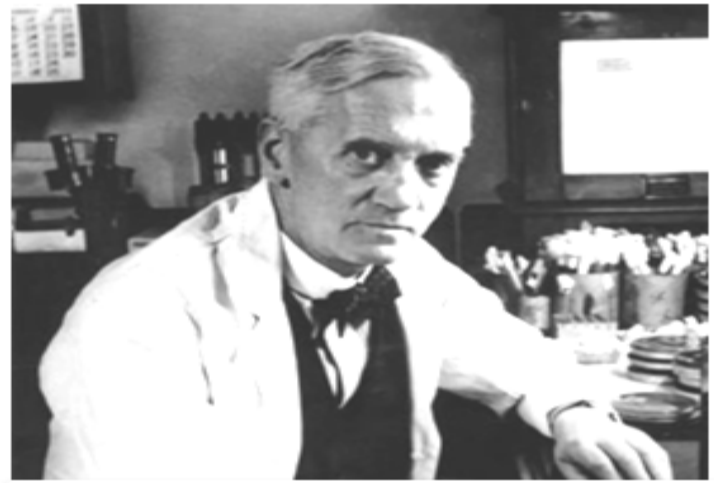
Carbapenems

Monobactams

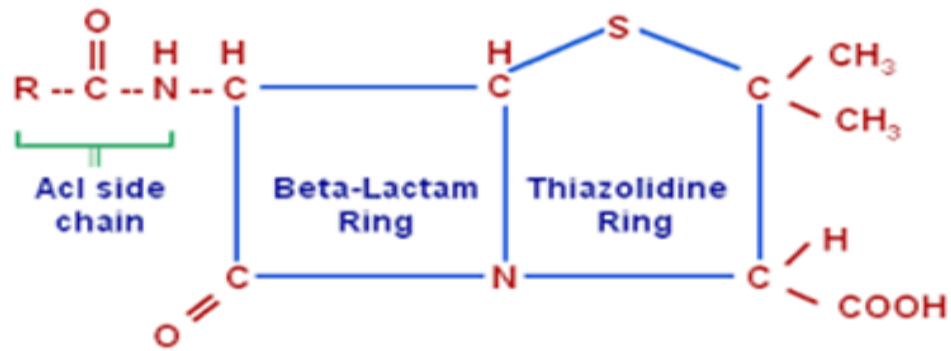
Penicillins

Chemistry:

- The basic structure of the penicillins consists of a **thiazolidine** ring (A) connected to a *β-lactam ring* (B) to which is attached a **side chain** (R).
- The β-lactam ring is responsible for the biological activity of penicillins, and it is targeted by organisms that produce penicillinase enzyme to destroy it.
- **The side chain** (R) can be cleaved by **amidase enzyme** producing **6-aminopenicillanic acid** to which new side chains can be added to produce new compounds of semi-synthetic penicillins.



Sir Alexander Fleming



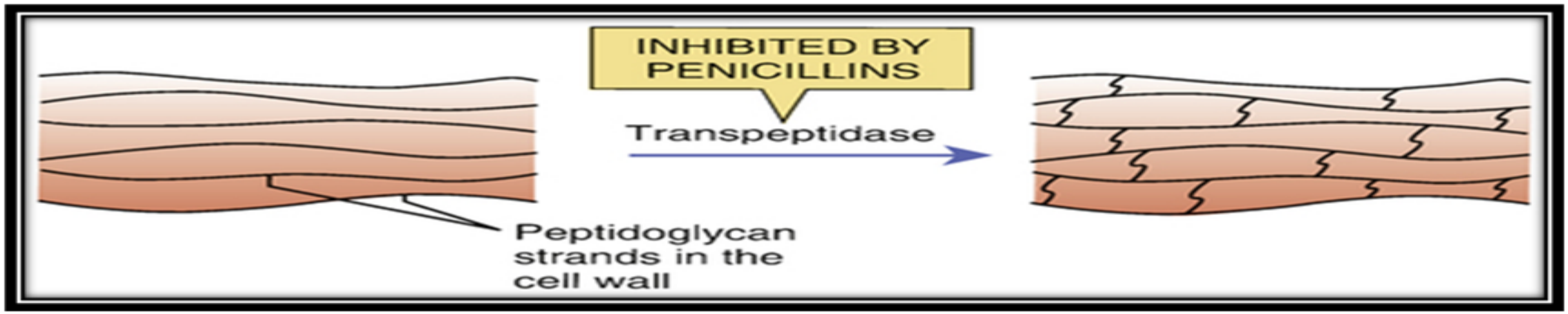
General Structure of Penicillins

Mechanism of action

➢Penicillins are **bactericidal** through inhibition of bacterial cell wall synthesis for growing bacteria.

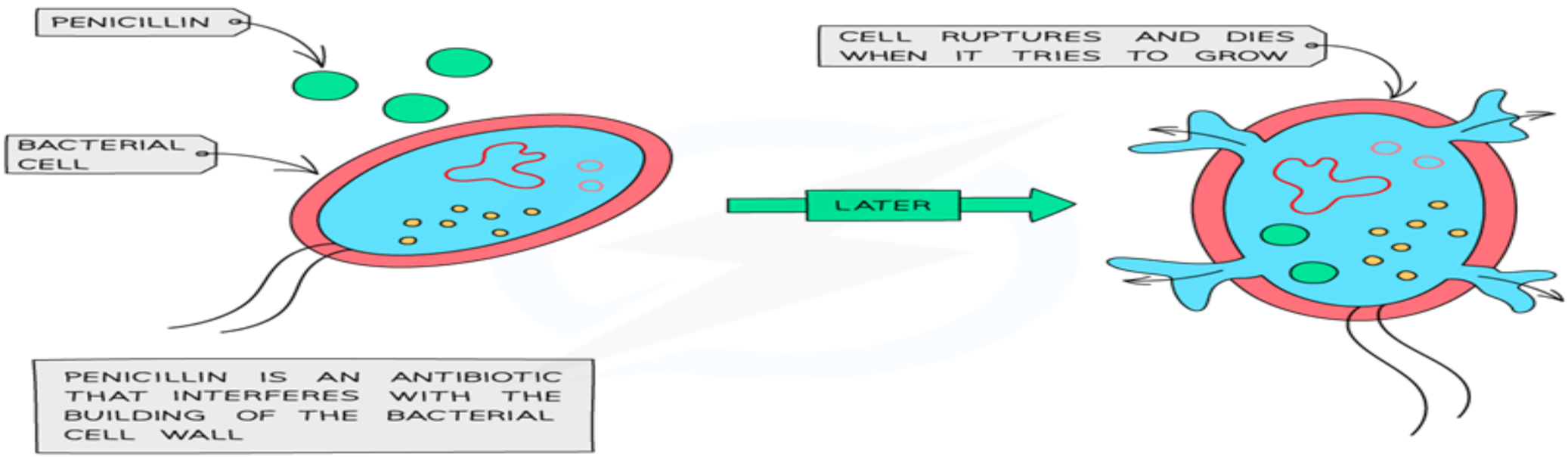
➢The bacterial cell wall consists of **glycopeptides** linked via five peptide bridges between amino acid side chains.

➢Bacterial cells with evident cell wall have penicillin binding proteins (**PBP**) to which transpeptidases are attached (in the **peri-plasmic space)**.



➢This **trans-peptidation reaction** gives the **rigid mechanical stability** of the cell wall and prevent osmotic shock.

➢Binding of Penicillins and other beta lactam drugs to PBP causes inhibition of these transpeptidases and inhibition cell wall synthesis occur leading to bacterial cell death.



Mechanism of resistance to penicillins

1. Enzymatic hydrolysis where bacteria produce β-lactamases (penicillinases) enzymes that can destroy β-lactam antibiotics.
2. Inability of the drug to penetrate to its site of action especially in gram negative bacteria.
3. Active efflux pumps that remove the antibiotic from its site of action.
4. Alteration in PBP with decreased affinity for β-lactam antibiotics.
5. Natural (intrinsic) resistance: in bacteria lacking cell wall like *Mycoplasma*..

Classification of the penicillins

According to spectrum

The PENICILLINS

Narrow spectrum penicillins
- Penicillin G
- Penicillin V

Broad Spectrum Penicillins (aminopenicillin)
- Amoxicillin
- Ampicillin
- Bacampicillin

Penicillinase-resistant Penicillin (anti-staphyloccocal penicillins)
- Cloxacillin
- Nafcillin
- Methicillin
- Dicloxacillin
- Oxacillin

Extended-Spectrum penicillins (Anti-pseudomonal penicillins)
- Carbenicillin
- Mezlocillin
- Piperacillin
- Ticacillin

1- Narrow spectrum (natural) penicillins

e.g. Natural Penicillins including **penicillin G (benzyl penicillin) & penicillin V (phenoxymethyl penicillin):**

➢Highly active against sensitive strains of **gram-positive cocci**, but they are readily **hydrolyzed by penicillinase**.

➢They are ineffective against most strains of Staph. aureus.

➢Some gram-negative cocci and anaerobic bacteria are **susceptible** to natural penicillins.

2- The penicillinase resistant penicillins (Anti-staph penicillins)

e.g. Methicillin, Nafcillin, Oxacillin, Cloxacillin, and Dicloxacillin.

➢They have very narrow spectrum (only active against sensitive strains of staphylococci), so, they are the agents of first choice for treatment of penicillinase-producing Staph aureus and Staph epidermidis that are not Methicillin resistant.

➢**They are ineffective against bacilli and gram-negative organisms.**

3- Broad spectrum penicillins (Aminopenicillins) e.g. **ampicillin** and **amoxicillin** which antimicrobial activity covers not only gram-positive cocci but also the gram-negative organisms like Hemophilus influenza, E coli and proteus mirabilis.
These drugs are administered frequently with a β-lactamase inhibitor such as clavulanate or sulbactam to prevent hydrolysis by class A β-lactamases.

4- Extended spectrum penicillins (Anti-pseudomonal penicillins)
like Carbenicillin, Mezlocillin, piperacillin and ticarcillin

Their antimicrobial activity extends to include the *Pseudomonas*, Enterobacter and proteus species as gram negative organisms.

They are destroyed by beta lactamases.

I- Natural penicillins

Pharmacokinetics:

- **Penicillin G** is not used orally (acid labile) and is usually given by Intravenous (IV) or intramuscular (IM) injection.
- **Penicillin V** is more stable in acidic medium and better absorbed from GIT after oral administration.
- They are short acting (**$t_{1/2}$ is 30 minutes**) which need frequent administration. .
- Penicillin G **penetrates** readily **inflamed meninges** to enter the CSF compared with normal meninges.
- Excretion is mainly by the kidney **(10% via glomerular filtration & 90% by active tubular secretion).**

- To prolong the duration of action and reduce the frequency of penicillin G injection, **probenecid** may be given as it blocks renal tubular secretion of penicillin (but rarely used for this purpose).

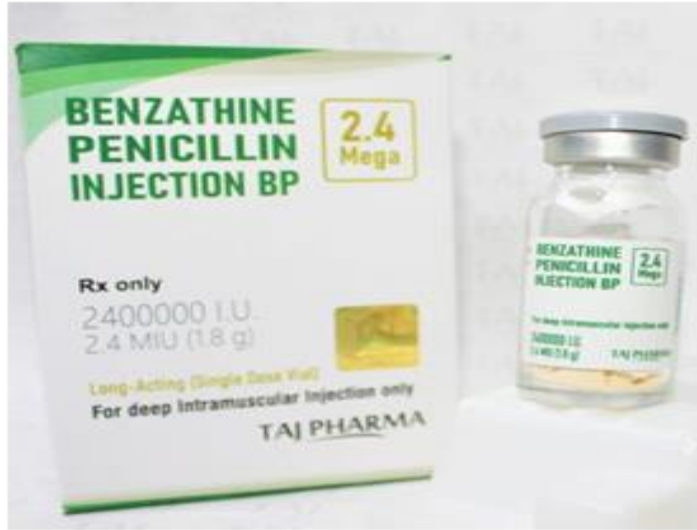
Long-acting penicillin

➢The **repository preparations of penicillin G** (e.g., penicillin G benzathine) are frequently used in clinical practice.

➢These **I.M**. preparations release penicillin G slowly from the area in which it is injected and produces relatively low but persistent concentrations of antibiotic in the blood.

➢Penicillin G benzathine preparation is given **once per month** as a prophylaxis in rheumatic fever.

➢Penicillin procaine is another repository form (long acting) of penicillin but given **I.M./12 hours.**



Therapeutic uses of penicillin G

1. **Pneumococcal** infection: pneumonia and meningitis.
2. **Streptococcal** infection such as pharyngitis caused by β-hemolytic streptococci. This prevents development of acute rheumatic fever, but not glomerulonephritis.

Penicillin plus aminoglycoside for treatment of streptococcal endocarditis.

1. **Meningococcal** infection: in acute meningitis , but ineffective in meningococcal carrier state or prophylaxis.
2. **Gonococcal** infection, but ceftriaxone is an effective alternative.

5- Anaerobic infection: e.g. brain abscess (with metronidazole).

6- Syphilis.

7-Diphtheria: antitoxin is the only effective treatment, but penicillin G eliminates the carrier state.

8- Clostridia infections: gas gangrene.

9- Anthrax.

12- Chemoprophylaxis….

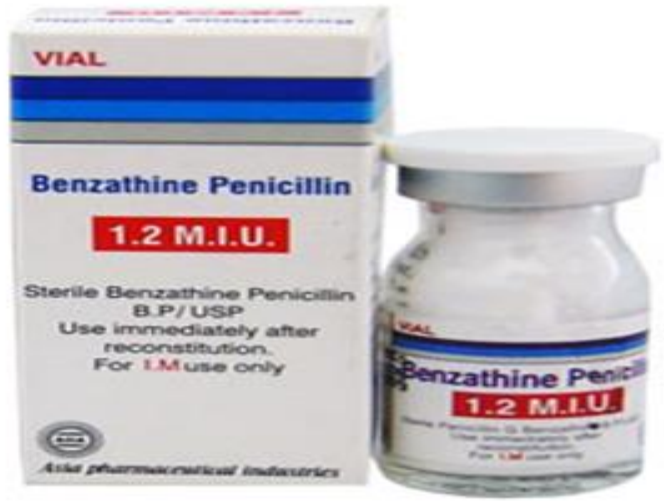
Chemoprophylaxis using Penicillin G and its long-acting preparations

Penicillin G is used for Prophylaxis in the following conditions:

1. **Recurrence of rheumatic fever. Benzathine penicillin** G (1.2 million units) given monthly as I.M. injection. In case of hypersensitivity to penicillin, sulfisoxazole or sulfadiazine or macrolides may be alternative.
2. Contact persons to patients suffering from **syphilis.**
3. Surgical or dental procedures in cardiac patients with rheumatic valve disease to guard against **sub-acute bacterial endocarditis infection (penicillin plus aminoglycoside).**

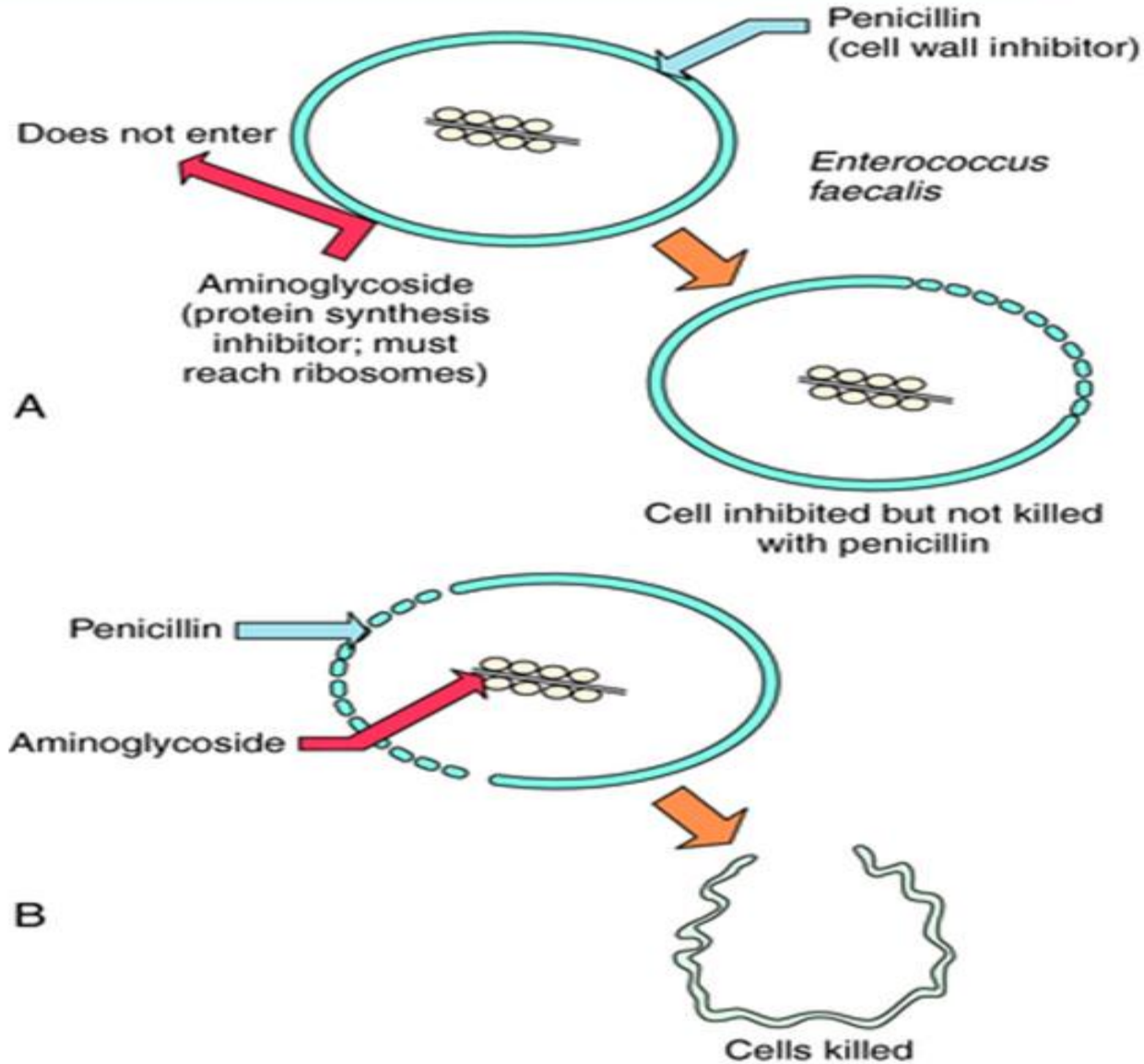
Doses of penicillin G

- The dose of penicillin G (4-24 million IU per day) given IV divided into 5 to 6 doses. **Each 1 million IU = 0.6 gram of penicillin G**.
- Benzathine penicillin G (**1.2 million IU**) IM (once every 3-4 weeks) is used to prevent recurrence of beta hemolytic streptococcal Infection among patients with rheumatic heart diseases to avoid recurrence of rheumatic fever.
- Benzathine penicillin G (**2.4 million IU**) IM (once every week for 3-4 weeks) can eradicate syphilis



The combination of penicillin and aminoglycoside

Penicillins and other cell wall inhibitors **facilitate the entry** of aminoglycoside into bacterial cells (**Synergism**)

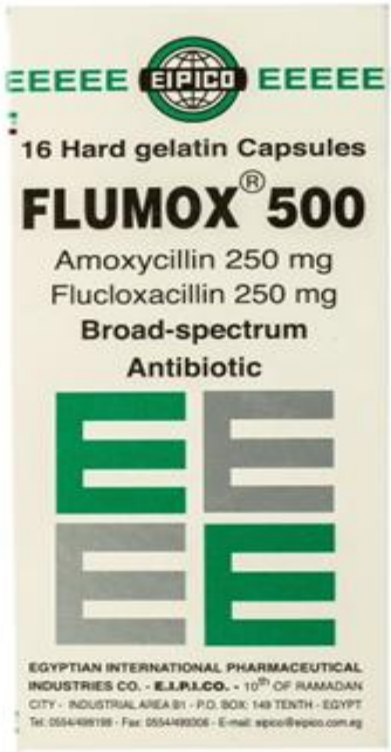


II- The penicillinase resistant (anti-staphylococcal) penicillins

Flucloxacillin, Nafcillin, Oxacillin, Cloxacillin, Dicloxacillin, and Methicillin

- They are resistant to hydrolysis by staphylococcal penicillinases; therefore, their use should be restricted to the treatment of infection caused by staphylococci.
- They are less effective against microorganisms susceptible to penicillin G .
- They have **no effect on gram negative bacteria** producing penicillinase.
- **Methicillin was withdrawn because of causing interstitial nephritis.**

- **Combination of flucloxacillin and amoxicillin are available as oral or injectable preparations.**
- **Also, combinations of dicloxacillin and ampicillin are available.**


EIPICO
16 Hard gelatin Capsules
FLUMOX® 500
Amoxycillin 250 mg
Flucloxacillin 250 mg
Broad-spectrum
Antibiotic
EGYPTIAN INTERNATIONAL PHARMACEUTICAL
INDUSTRIES CO. - E.I.P.I.CO. - 10th OF RAMADAN


EIPICO
VIAL
FLUMOX®
Amoxycillin
Flucloxacillin
1 g
Broad - Spectrum Antibiotic
For I.M. or I.V. injection
فلوموكس


AMPIWELL-DC
Rx
Ampicillin & Dicloxacillin Capsules
AMPIWELL-DC
Wellona Pharma
10X10 Capsules

Methicillin resistant microorganisms

➢Methicillin resistant microorganisms like **Methicillin-resistant Staph. aureus (MRSA)** is a term applied now to all bacteria which are resistant to all penicillinase resistant penicillins like Methicillin.

➢MRSA is resistant to most β-lactams because of the presence of mecA, a gene that produces a penicillin binding protein (PBP2a) with low affinity for β-lactam antibiotics

➢Vancomycin, linezolid and other drugs is indicated in these conditions although intermediate level of resistance is emerging.

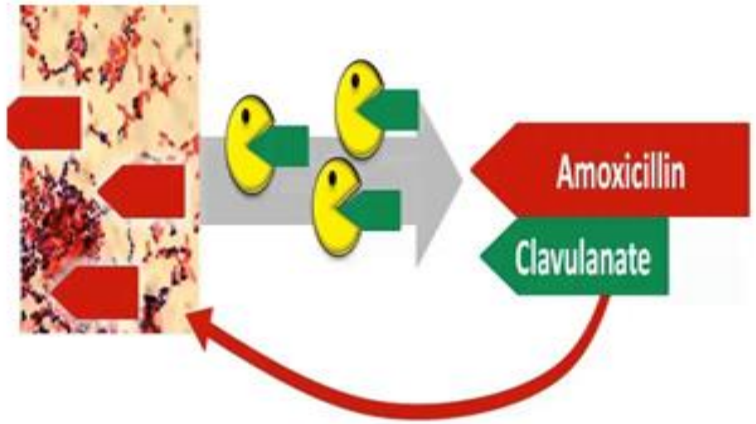
III- Aminopenicillins (broad spectrum penicillins)

Ampicillin & amoxicillin

➢ They are bactericidal for sensitive strains of **both gram positive and gram-negative bacteria.**

➢ They are destroyed by penicillinase enzyme, so, the concurrent administration of **β-lactamase inhibitors (clavulanate** or **sulbactam)** markedly expands the spectrum of activity of these agents (**synergism**).

➢ Oral and parental preparations are available.



Clavulanate, a "suicide inhibitor", is a way to block the bacterial resistance mechanism of β-lactamase

Therapeutic uses of Aminopenicillins

1- **Upper respiratory tract infection** (e.g. strept. tonsillitis, pharyngitis, otitis media, sinusitis ..etc.), and some lower respiratory infections (e.g. lobar pneumonia).

2- **Meningitis**: in combination with Vancomycin and a third-generation cephalosporin as empirical treatment to avoid resistance.

3- **Ampicillin** at high dose is effective also in shigellosis.

4- **Amoxicillin** is used with other drugs for eradication of **H. pylori infections.**

5- Augmentin (**Amoxicillin- clavulanate**) is indicated in treatment of mild cases of **cellulitis and diabetic foot infections.**

N.B. The use of **ampicillin** in treating **typhoid fever** & **Urinary tract infection** is limited now.

IV- Extended spectrum (Anti-pseudomonal) penicillins

carboxypenicillins and ureidopnicillins

➢The carboxypenicillins (**carbenicillin** and **ticarcillin**) and the ureidopenicillins (**mezlocillin** and **piperacillin**) have activity against *Pseudomonas aeroginosa* and certain *proteus* species that are resistant to ampicillin.

➢They are used for treating urinary tract infections and other infections caused by *Pseudomonas* and other gram-negative bacilli.

➢They are sensitive to destruction by β-lactamases. Adding beta lactamase inhibitor (e.g. tazobactam) would decrease bacterial resistance.

β-Lactamase inhibitors

- They inactivate β-lactamases. They are active against plasmid-encoded β-lactamases but not against type I chromosomal β-lactamases induced by gram negative bacilli.
- Examples are **clavulanic acid** and **sulbactam**.
- These compounds are **suicide inhibitors** that **irreversibly** bind to β-lactamases **protecting beta lactam drugs** from hydrolysis & **synergism** occurs.

- **Augmentin = Amoxicillin + clavulanic acid**
- **Unasyn = Ampicillin + sulbactam**
- **Timentin= ticarcillin +Clavulanic acid**
- ***Zosyn= piperacillin+ tazobactam***


Thank
YOU