بسم الله الرحمن الرحيم

Pharmacology
Lecture 28-Anti bacterial drugs (IV)
Cell wall inhibitors
(Penicillins)

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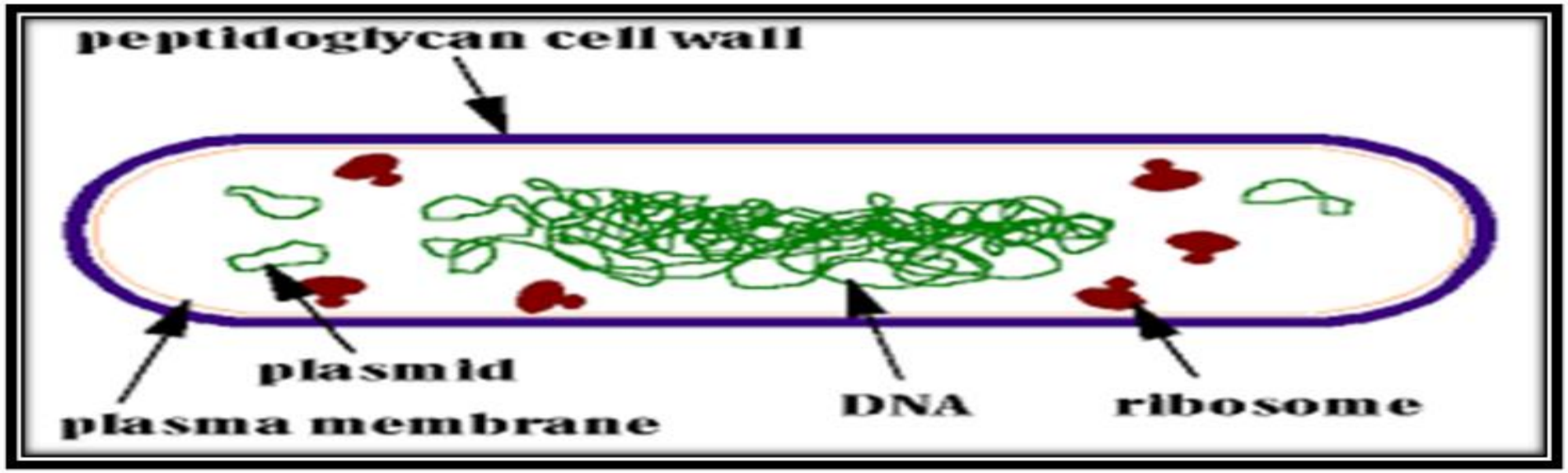
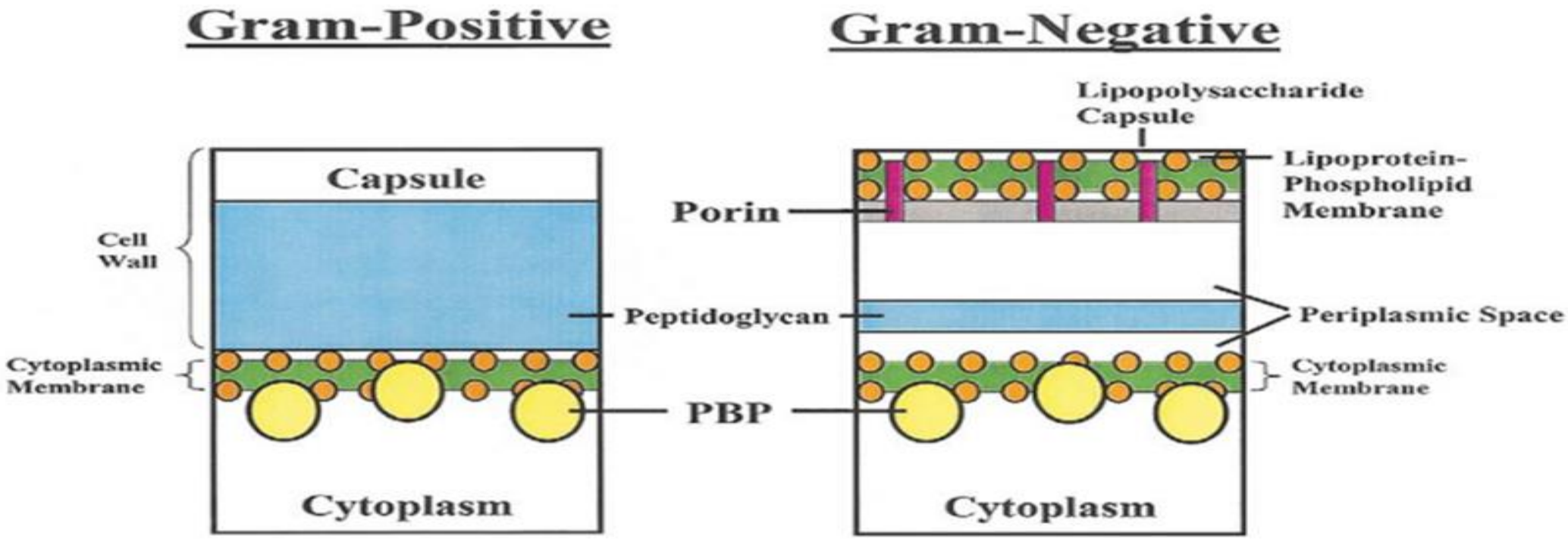
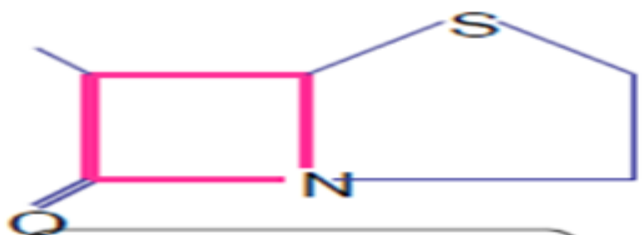
2023


peptidoglycan cell wall
plasmid
plasma membrane
DNA
ribosome

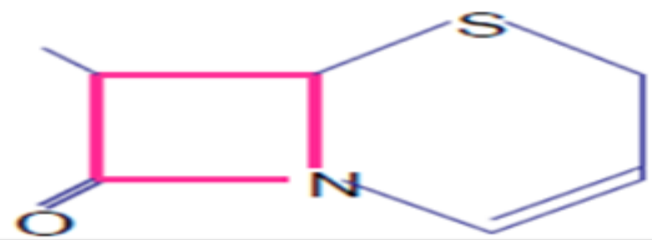

Gram-Positive
Gram-Negative
Capsule
Cell Wall
Peptidoglycan
Cytoplasmic Membrane
PBP
Cytoplasm
Lipopolysaccharide Capsule
Porin
Lipoprotein-Phospholipid Membrane
Periplasmic Space
Cytoplasmic Membrane
Cytoplasm

Beta lactam antibacterial drugs

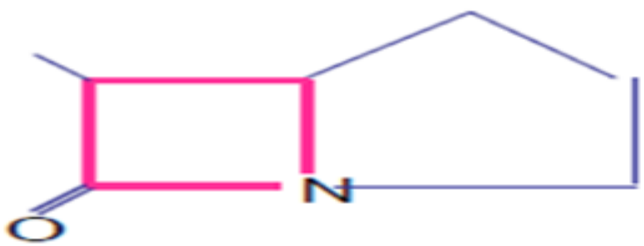
The β-lactams include **penicillins**, **cephalosporins, monobactams** and **carbapenems** and they share a common structure, and a common mechanism of action.



Penicillins



Cephalosporins



Carbapenems

Monobactams

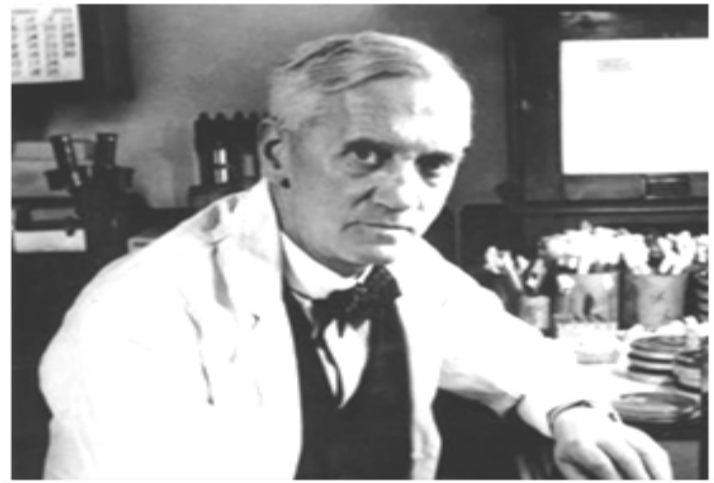
Features of beta lactam antibiotics:

- They contain the **4-membered ring** (**lactam**) which is intrinsically labile to **hydrolysis** (*acidic* or *enzymatic*).
- **Target:** cell-wall biosynthesis
- **Action:** bactericidal, active only against *growing cells.*
- They have variable spectrum.

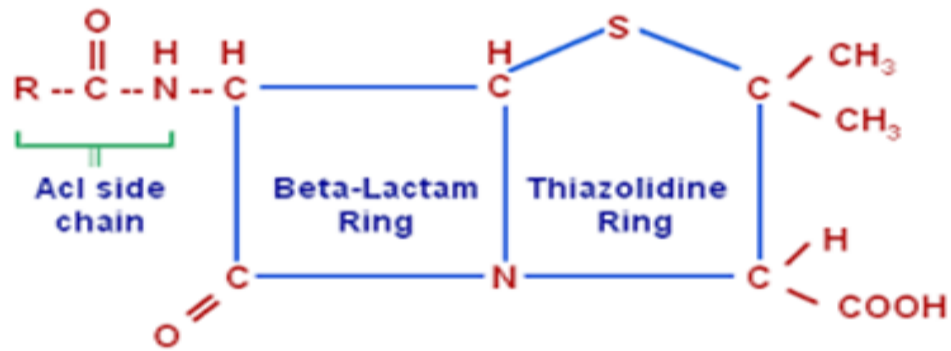
Penicillins

Chemistry:

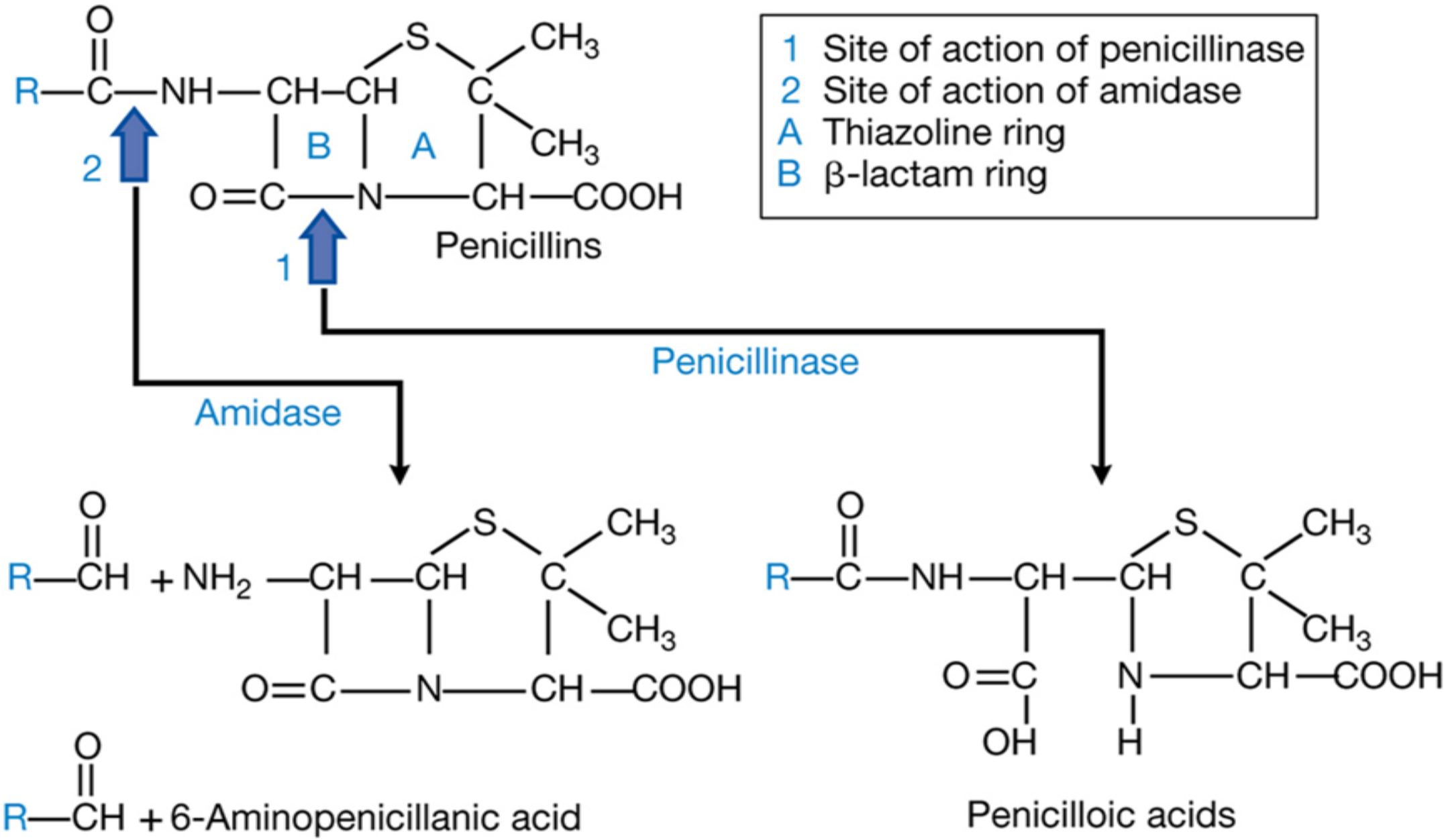
- The basic structure of the penicillins consists of a **thiazolidine** ring (A) connected to a *β-lactam ring* (B) to which is attached a **side chain** (R).
- The β-lactam ring is responsible for the biological activity of penicillins, and it is targeted by organisms that produce penicillinase enzyme 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

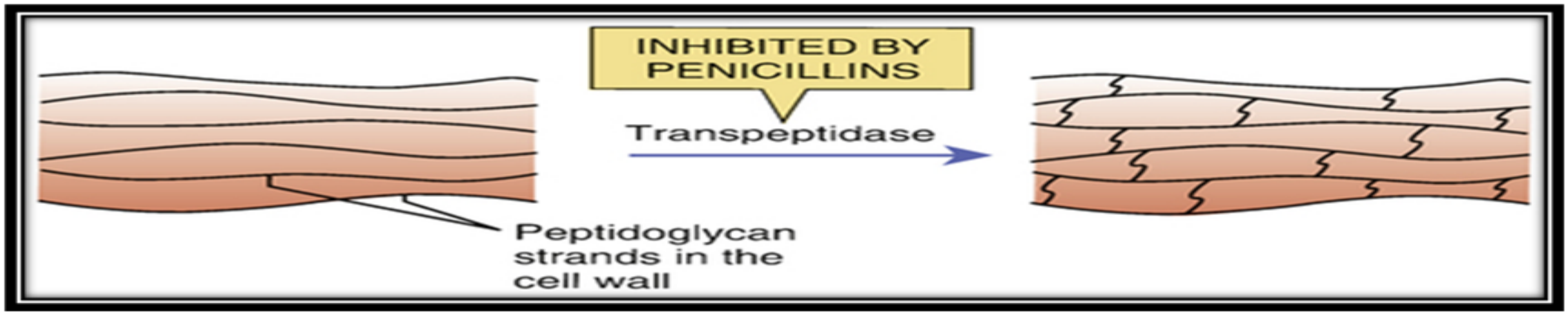

1 Site of action of penicillinase
2 Site of action of amidase
A Thiazoline ring
B β-lactam ring
Penicillins
Penicillinase
Amidase
+ 6-Aminopenicillanic acid
Penicilloic acids

Mechanism of action

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

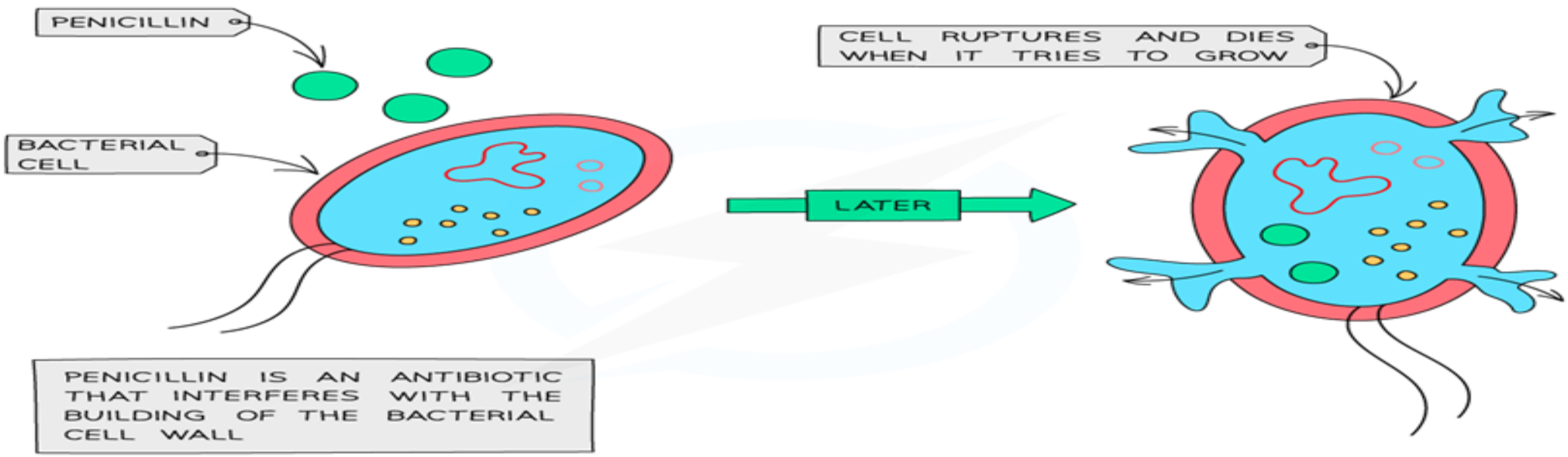
➢The bacterial cell wall consists of **glycopeptides** linked via five peptide bridges between amino acid side chains.

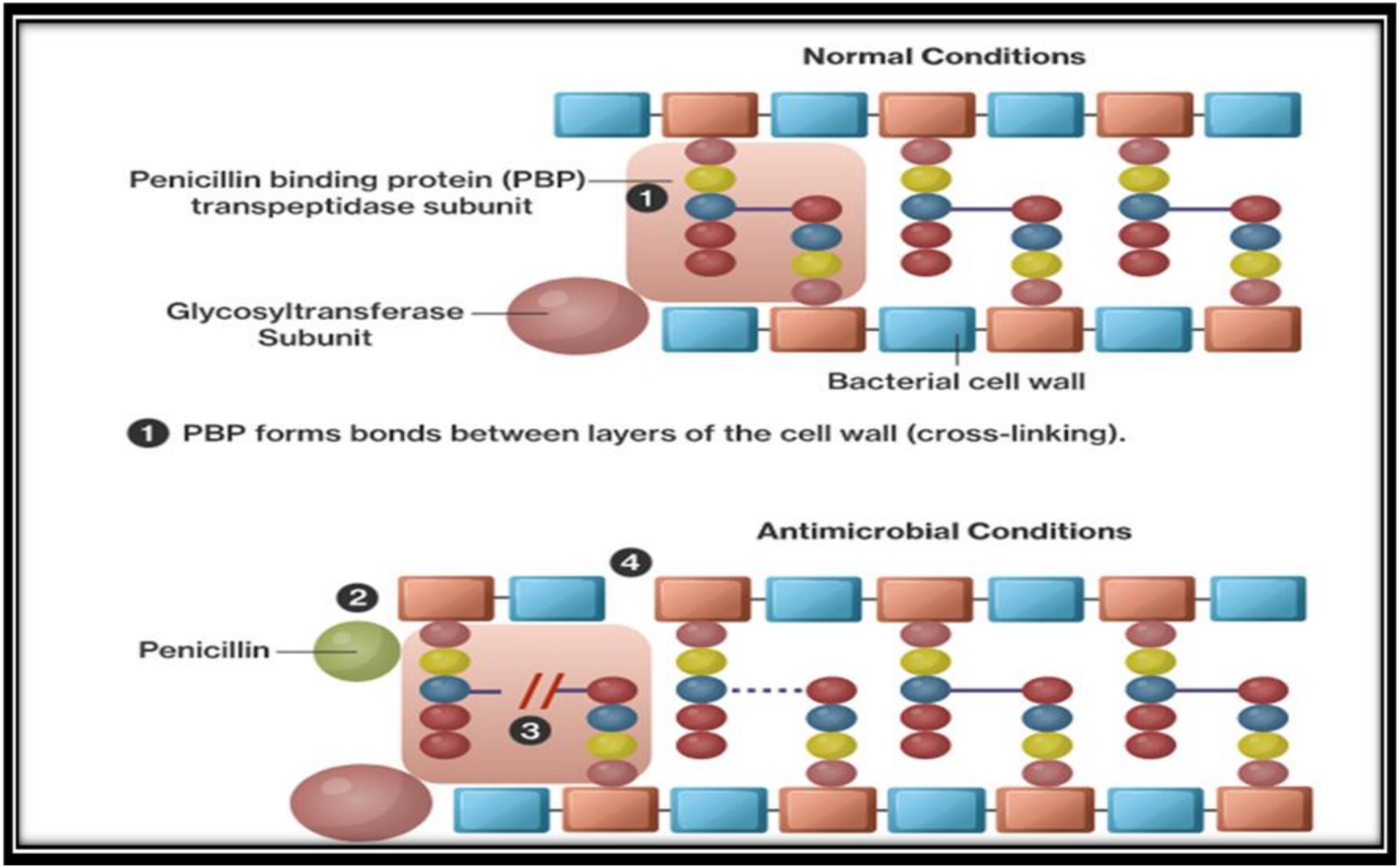
➢Bacterial cells with evident cell wall have penicillin binding proteins (**PBP**) to which transpeptidases are attached (in the **peri-plasmic space)**.

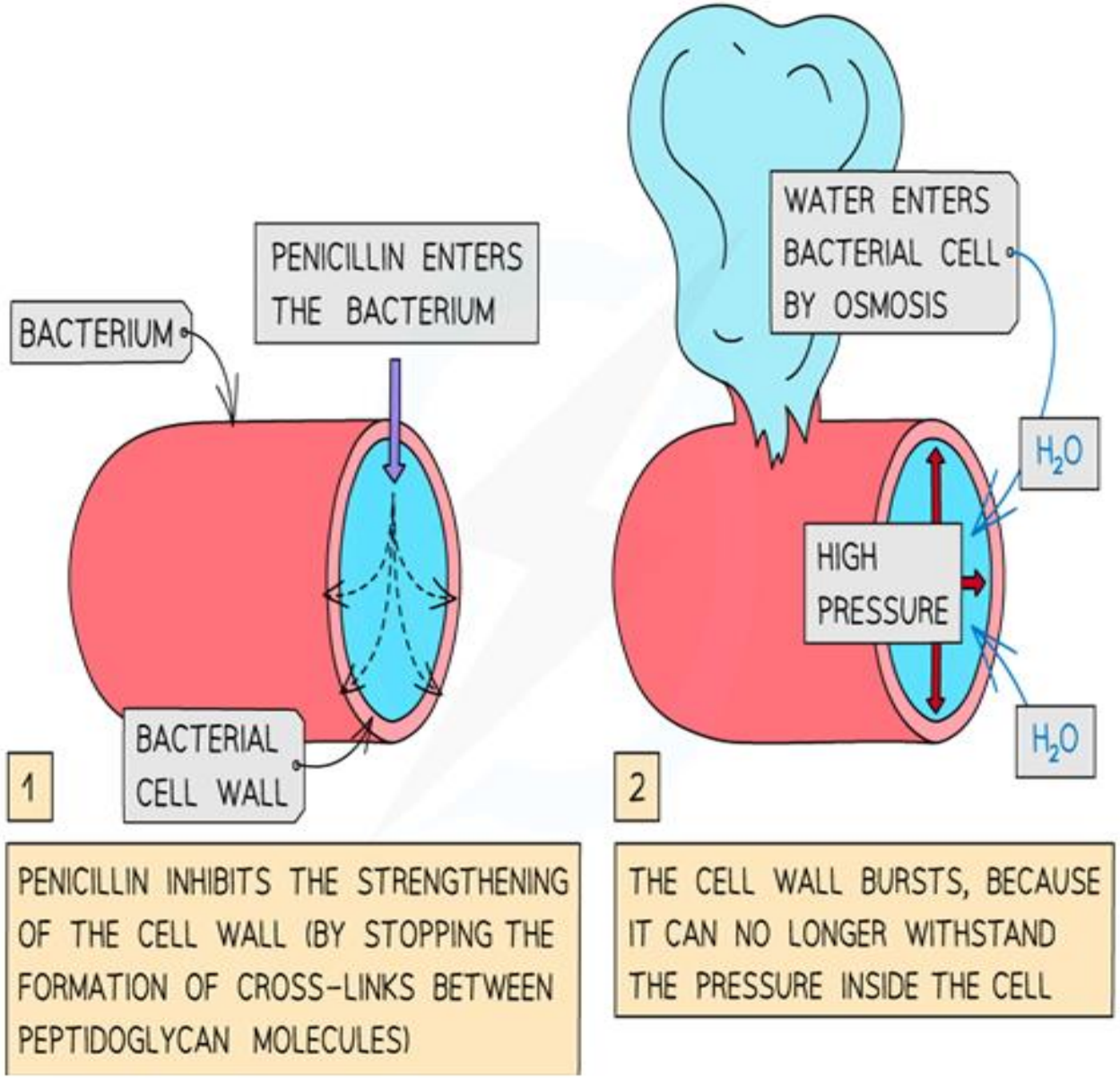


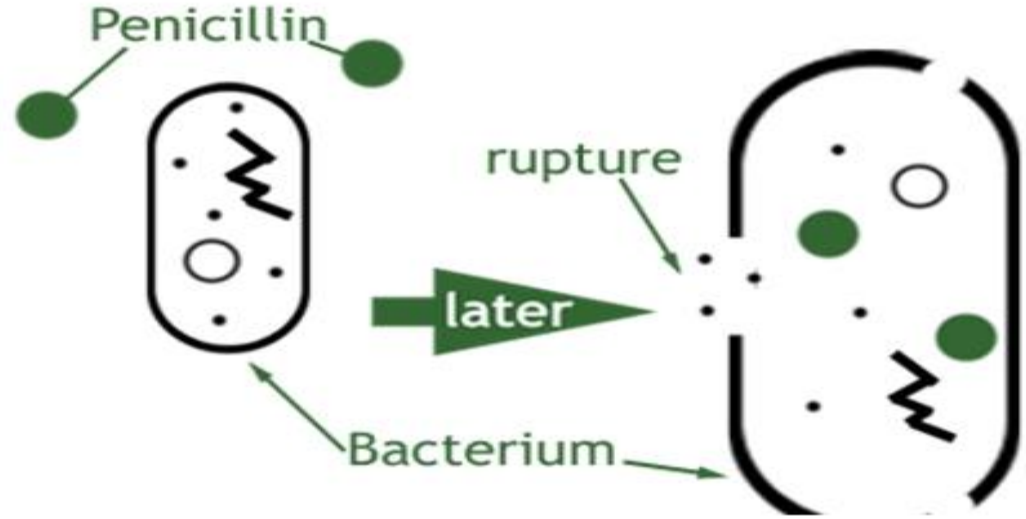
➢This **trans-peptidation reaction** gives the **rigid mechanical stability** of the cell wall and prevent osmotic shock.

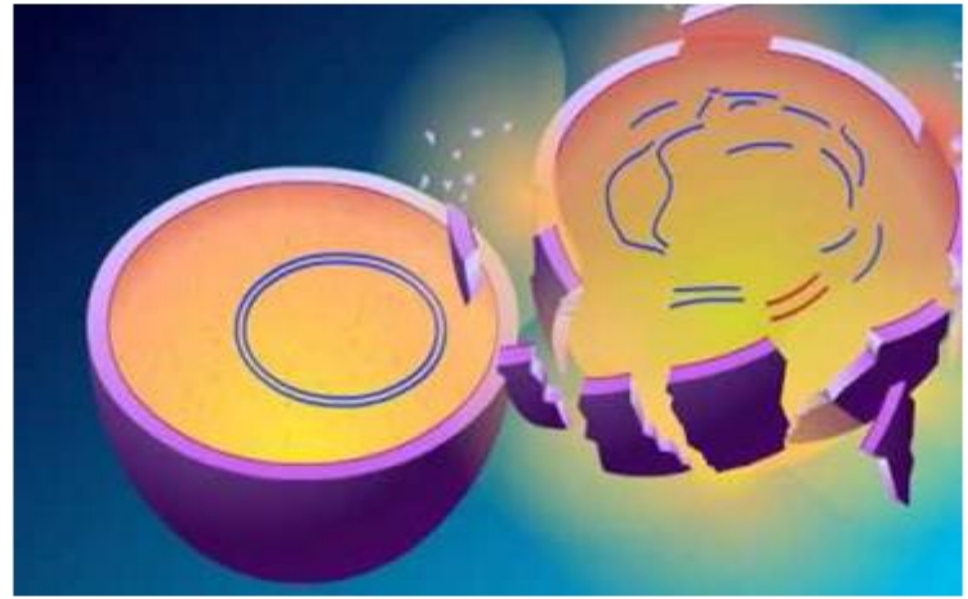
➢Binding of Penicillins and other beta lactam drugs to PBP causes inhibition of these transpeptidases and inhibition cell wall synthesis occur leading to bacterial cell death.




Normal Conditions
Penicillin binding protein (PBP)
transpeptidase subunit
1
Glycosyltransferase
Subunit
Bacterial cell wall
1 PBP forms bonds between layers of the cell wall (cross-linking).
Antimicrobial Conditions
4
2
Penicillin
3

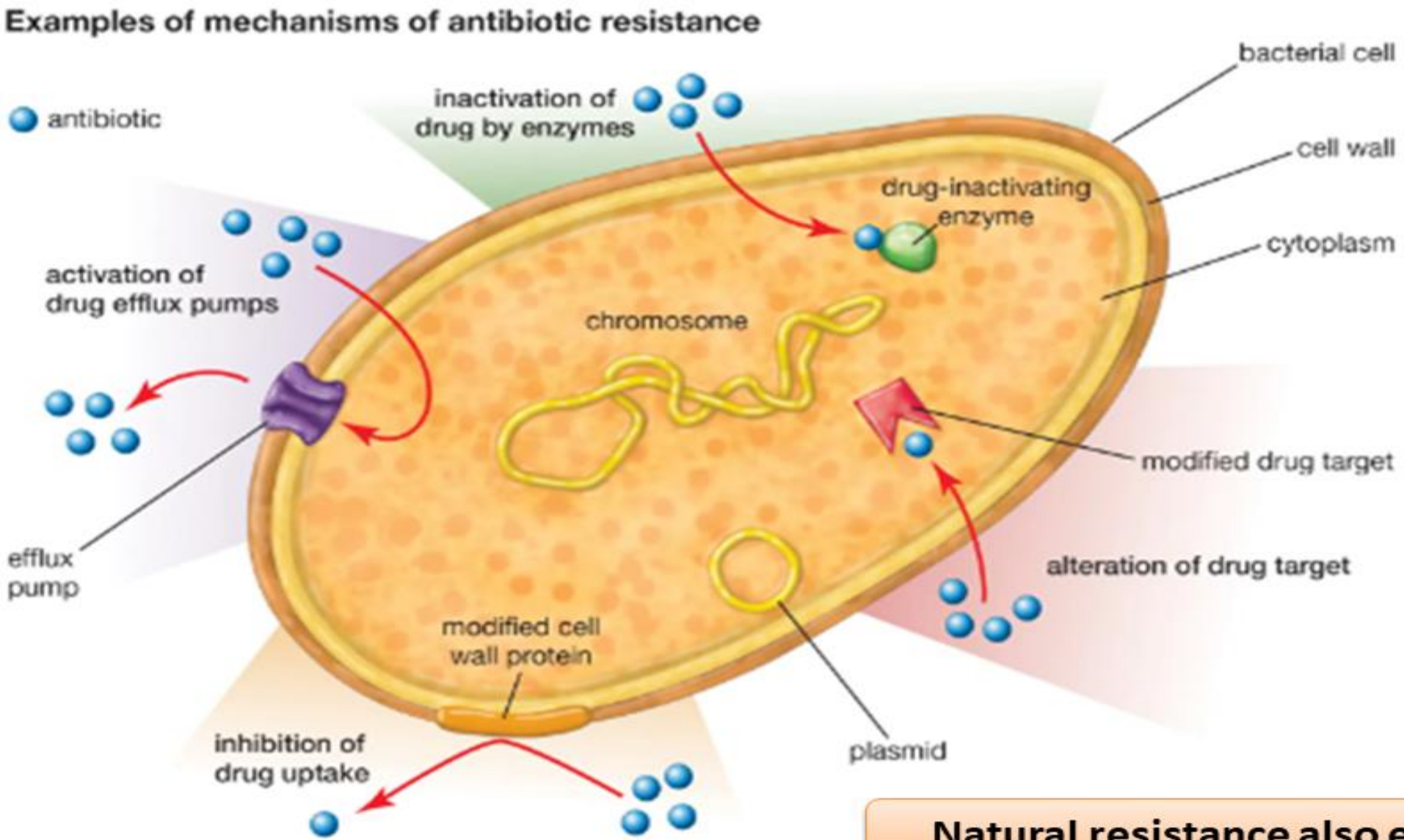

BACTERIUM
PENICILLIN ENTERS THE BACTERIUM
BACTERIAL CELL WALL
1
PENICILLIN INHIBITS THE STRENGTHENING OF THE CELL WALL (BY STOPPING THE FORMATION OF CROSS-LINKS BETWEEN PEPTIDOGLYCAN MOLECULES)
WATER ENTERS BACTERIAL CELL BY OSMOSIS
H_2O
HIGH PRESSURE
H_2O
2
THE CELL WALL BURSTS, BECAUSE IT CAN NO LONGER WITHSTAND THE PRESSURE INSIDE THE CELL


Penicillin
rupture
later
Bacterium

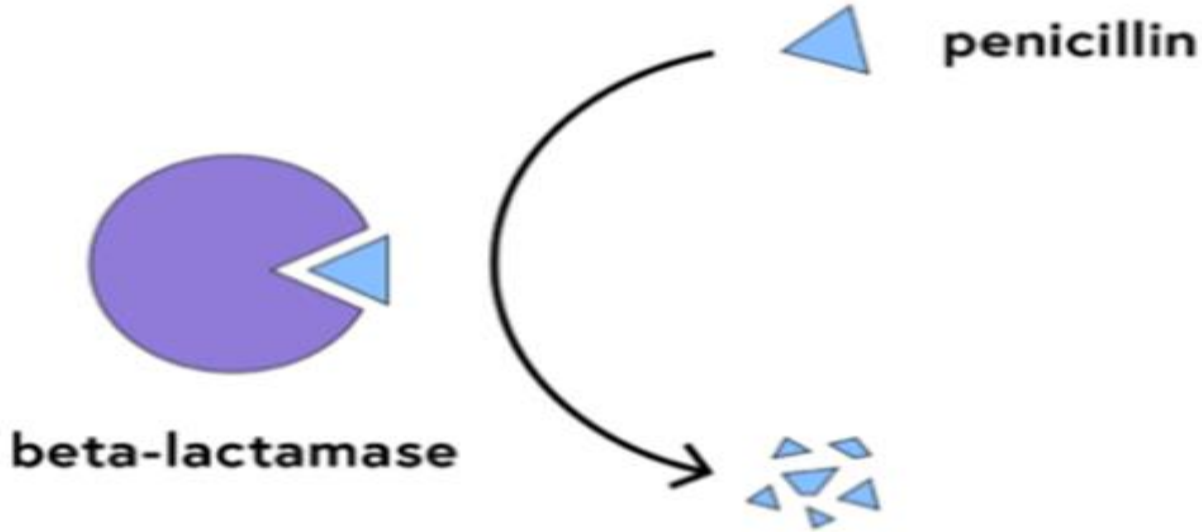


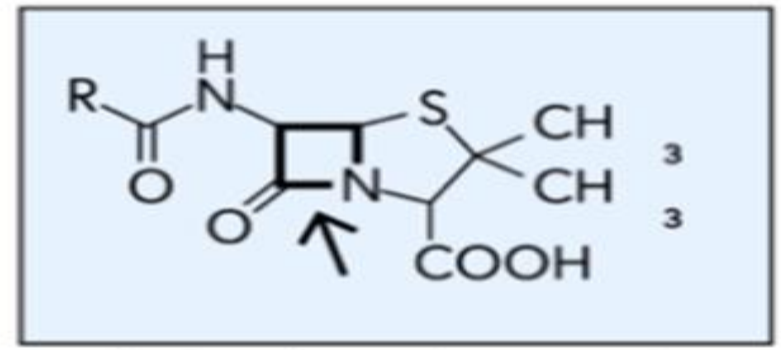
Mechanism of resistance to penicillins

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*..

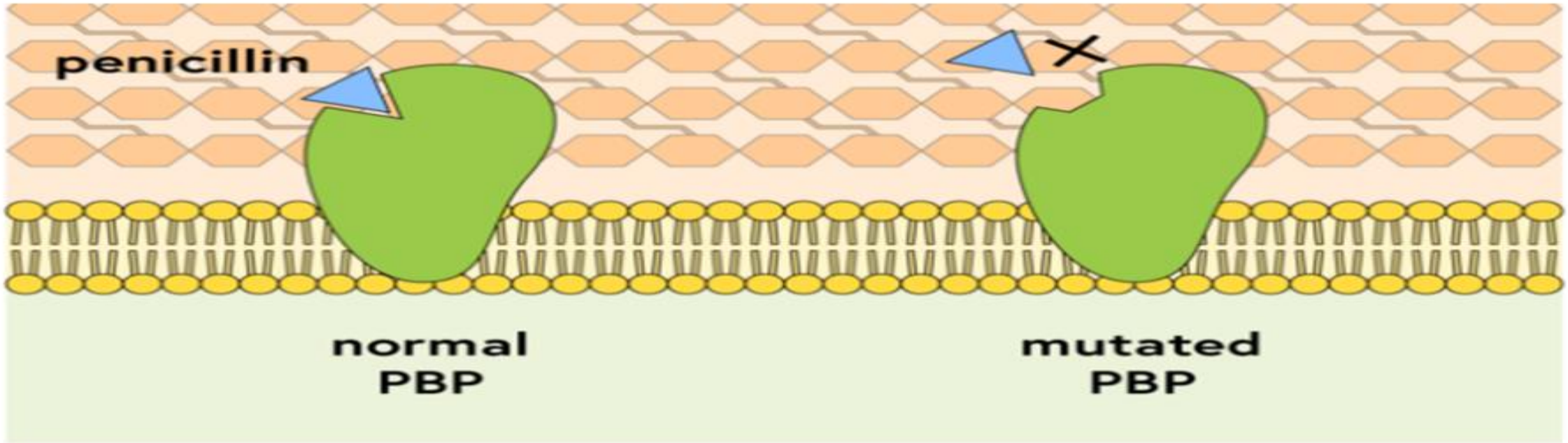


Natural resistance also exist





degradation beta-lactam ring



Classification of the penicillins

According to spectrum

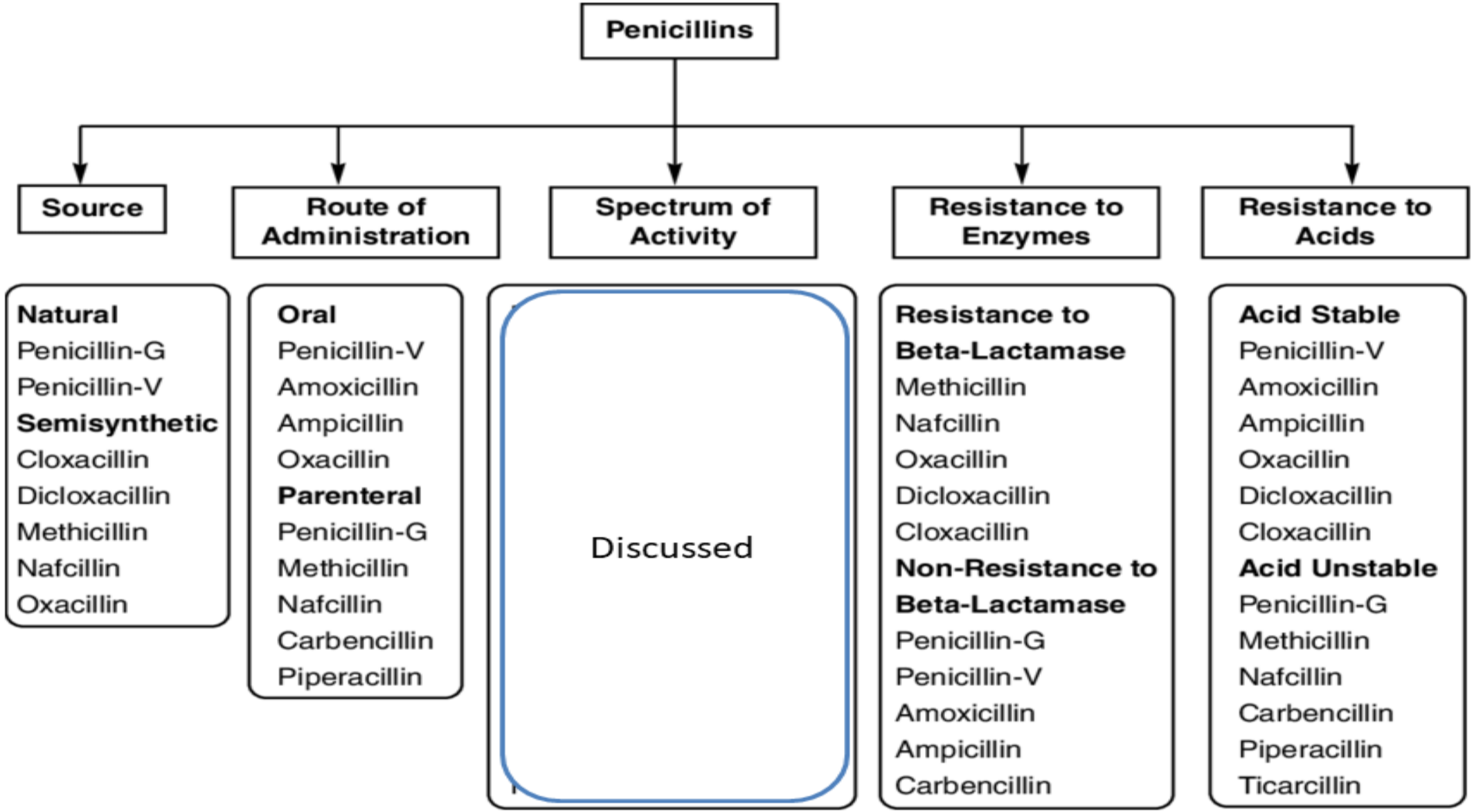
The PENICILLINS

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


Penicillins
Source
Route of Administration
Spectrum of Activity
Resistance to Enzymes
Resistance to Acids
Natural
Penicillin-G
Penicillin-V
Semisynthetic
Cloxacillin
Dicloxacillin
Methicillin
Nafcillin
Oxacillin
Oral
Penicillin-V
Amoxicillin
Ampicillin
Oxacillin
Parenteral
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Discussed
Resistance to Beta-Lactamase
Methicillin
Nafcillin
Oxacillin
Dicloxacillin
Cloxacillin
Non-Resistance to Beta-Lactamase
Penicillin-G
Penicillin-V
Amoxicillin
Ampicillin
Carbencillin
Acid Stable
Penicillin-V
Amoxicillin
Ampicillin
Oxacillin
Dicloxacillin
Cloxacillin
Acid Unstable
Penicillin-G
Methicillin
Nafcillin
Carbencillin
Piperacillin
Ticarcillin

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:

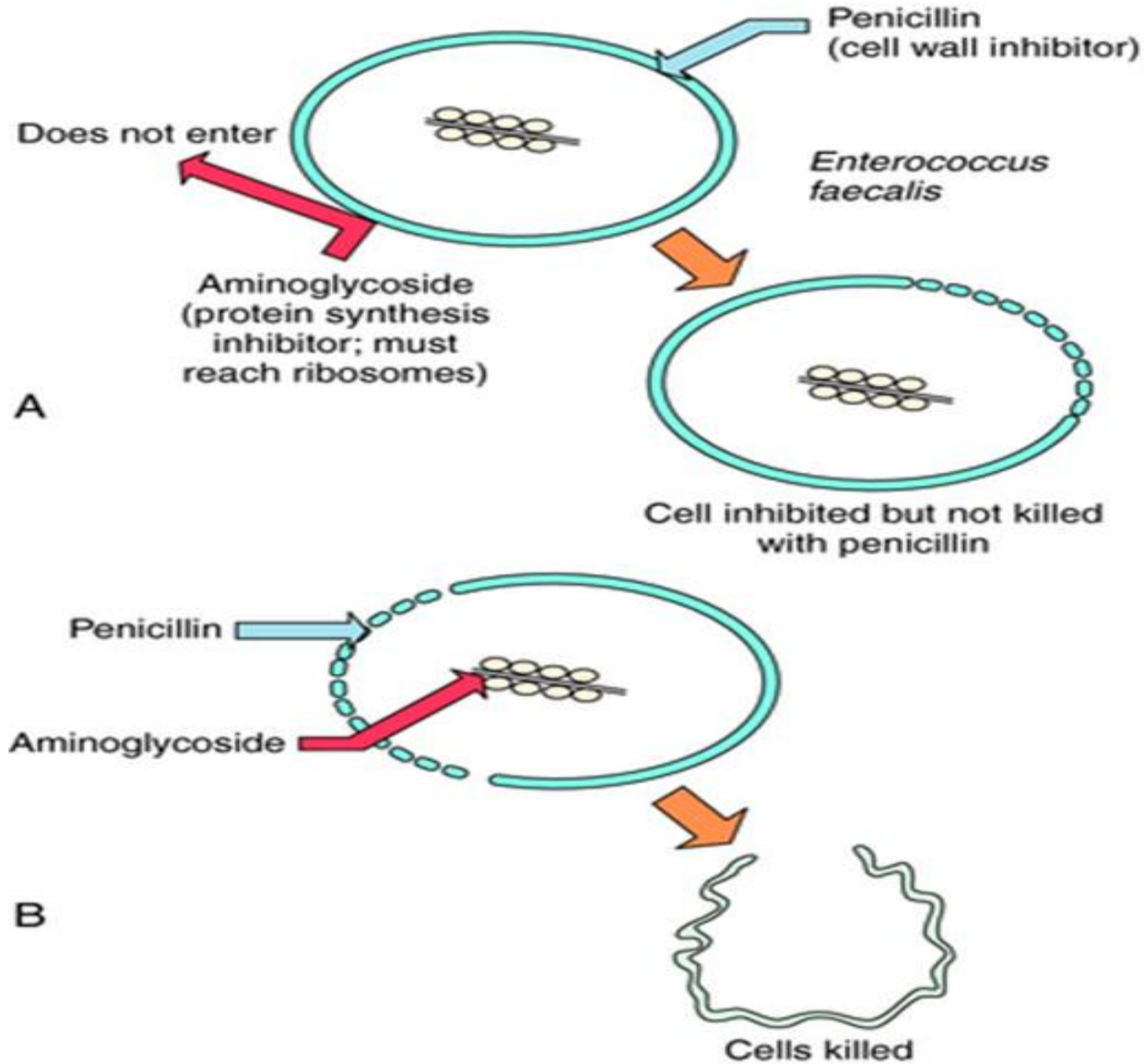
1. **Recurrence of rheumatic fever. Benzathine penicillin** G (1.2 million units) given monthly as I.M. injection. In case of hypersensitivity to penicillin, sulfisoxazole or sulfadiazine or macrolides may be alternative.
2. Contact persons to patients suffering from **syphilis.**
3. Surgical or dental 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**)

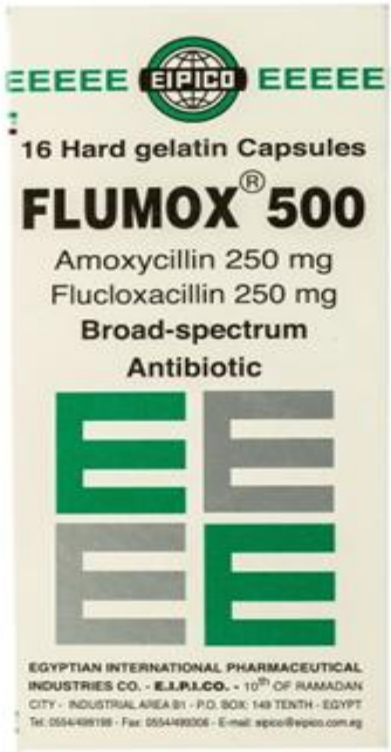


II- The penicillinase resistant (anti-staphylococcal) penicillins

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

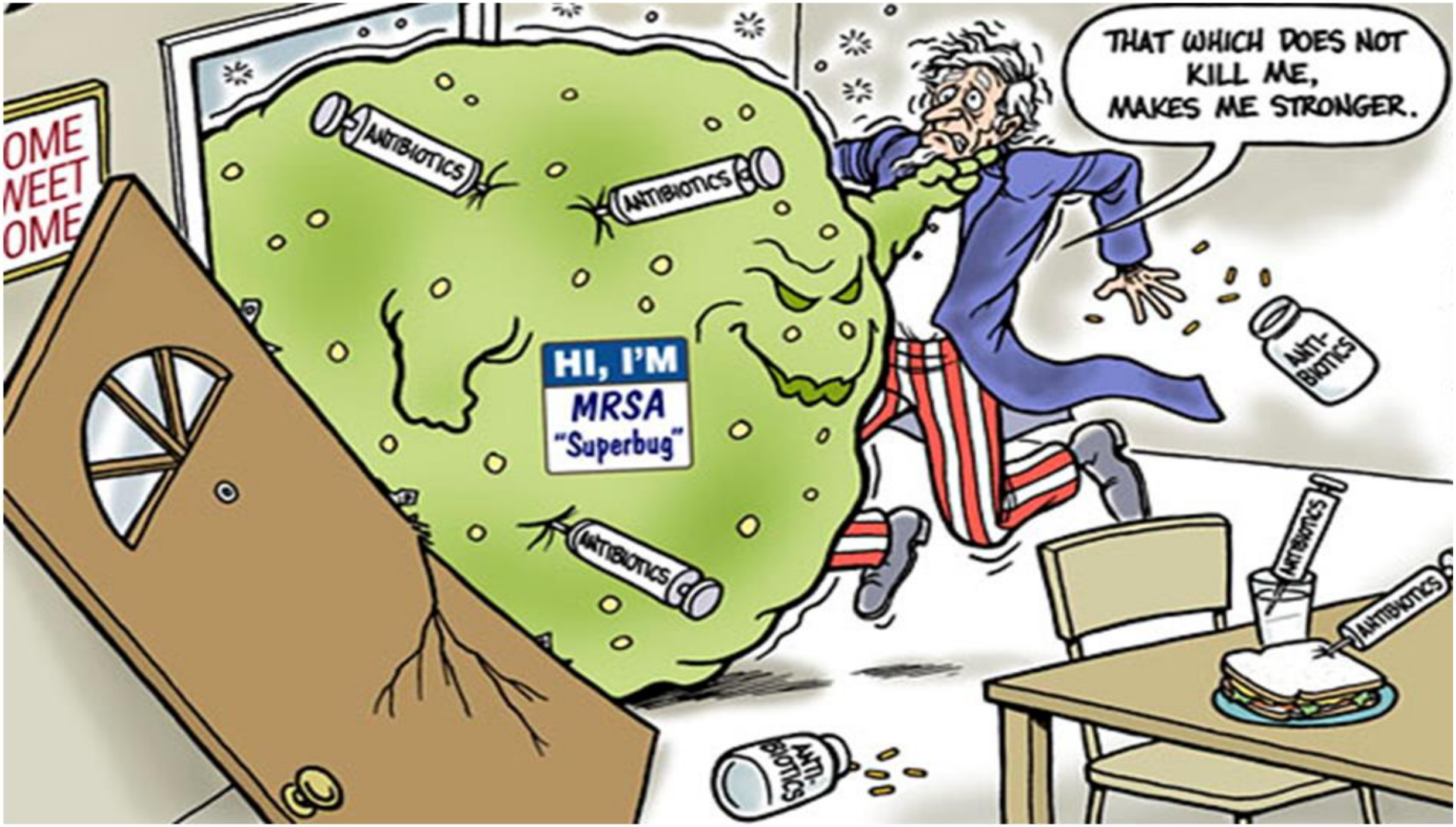

AMPIWELL-DC
Rx
Ampicillin & Dicloxacillin Capsules
AMPIWELL-DC
Wellona Pharma
10X10 Capsules

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.


OME
NEET
OME
ANTIBIOTICS
ANTIBIOTICS
HI, I'M
MRSA
"Superbug"
ANTIBIOTICS
THAT WHICH DOES NOT KILL ME, MAKES ME STRONGER.
ANTI-BIOTICS
ANTIBIOTICS
ANTIBIOTICS
ANTI-BIOTICS

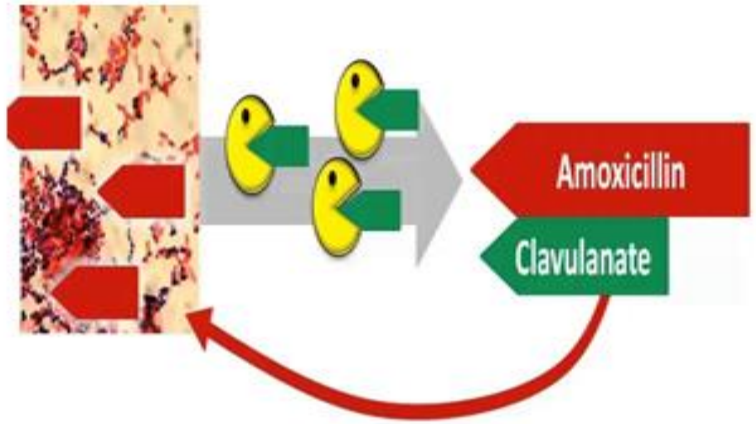
III- Aminopenicillins (broad spectrum penicillins)

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***

Adverse reactions to penicillins

1-Hypersensitivity reactions:

The reactions may be presented as maculopapular **rash**, **urticarial** rash, **fever**, **bronchospasm**, **vasculitis**, interstitial **nephritis**, serum sickness, **exfoliative dermatitis** and **Steven Johnson syndrome**.

The most serious reactions are **angioedema** (marked swelling of the face, tongue, lips and peri-orbital tissues accompanied commonly by asthmatic breathing) and **anaphylactic shock** (the dramatic scenario of sudden severe hypotension and rapid death). Incidence of anaphylaxis with IM penicillin is **0.05%.**

Stevens–Johnson syndrome

➢**Hemolytic anemia,** and **eosinophilia**, may occur. Drug Reaction with Eosinophilia and Systemic Symptoms (**DRESS**) syndrome is rare with beta lactams but sometimes fatal.

➢The incidence of all allergic reactions is about **0.7-10%** and cross hypersensitivity to the other β-lactams (e.g. cephalosporins, some carbapenems) occurs sometimes.

➢ The reactions may occur **with any dose and dosage form** of penicillin (not dose-dependent but individual dependent).

➢It is not necessary to be preceded by known previous exposure to penicillins as drugs. Unrecognized exposure to penicillin may occur in the environment e.g. in foods of animal origin or from the organisms-producing penicillins.

➢Penicillins and their breakdown products (penicilloyl moiety) act as haptens to which antibodies (IgE) are formed.

DRESS syndrome (previously called drug induced pseudo-lymphoma)

Hematologic abnormalities
- Eosinophilia >1500/mm^3
- Presence of atypical lymphocytes

Systemic involvement
- Adenopathies >2 cm in diameter
- Cytolytic hepatitis
- Interstitial nephritis
- Interstitial pneumonitis
- Myocarditis

➢ Taking **history** of hypersensitivity and doing **skin testing** before administration of penicillins can reduce the incidence of these reactions (namely anaphylaxis).

➢If necessary (e.g., treatment of **enterococcal endocarditis** or **neurosyphilis** in a patient with serious penicillin allergy), **desensitization** can be accomplished with gradually increasing doses of penicillin.

2- Jarisch Herxheimer reaction (JHR):

➢JHR is a transient clinical phenomenon that occurs in patients infected by spirochetes who undergo antibiotic treatment.

➢ More specifically, the reaction occurs within 8-24 hours of antibiotic therapy for spirochetal infections, including syphilis, leptospirosis, Lyme disease, and relapsing fever.

- It usually manifests as fever, chills, rigors, nausea and vomiting, headache, tachycardia, hypotension, hyperventilation, flushing, myalgia, and exacerbation of skin lesions.

- JHR is an acute, self-limiting condition, which is important to identify in patients and to **distinguish it from allergic reactions and sepsis.**

- The breakdown of the spirochete after the use of antibiotics causes the **release of toxins and cytokines** (TNF alpha, IL6 and IL8).

- TNF-alpha antibodies and, in some cases, **steroids** as well can ameliorate the reaction while **paracetamol** of limited efficacy.

3- Acute generalized exanthematous pustulosis (AGEP):

- AGEP, is an uncommon pustular drug eruption characterized by sterile superficial pustules.
- AGEP is usually classified as a **severe cutaneous adverse reaction.**
- Over 90% of cases of AGEP are provoked by medications, most often beta-lactam antibiotics (e.g., penicillins, cephalosporins).
- AGEP is associated with *IL36RN* **gene mutations**.
- These genetic abnormalities make the patient more susceptible to pustulosis when receive certain medications or viral infection.
- Treatment includes supportive care, prevention of the culprit antibiotics and the use of a potent topical steroid.

3- Other adverse effects:

1-Pain and sterile inflammation at the sites of I.M. injections.

2-Nausea, vomiting and diarrhea (dose related when given orally).

3-Carbenecillin may impair platelet aggregation and its sodium salt precipitate heart failure (withdrawn from market).

4-In renal insufficiency, parenteral administration of large doses of penicillin G may produce **seizures.**

5- Alteration of normal intestinal flora when given by mouth may cause **super-infection** like oral candidiasis or pseudomembranous colitis (clostridial).

6- Nafcillin can cause neutropenia and nephritis.

7- Oxacillin may cause hepatitis.

8- Amoxicillin related maculopapular rash:

- About 5% to 10% of children will develop a morbilliform rash.
- The amoxicillin -related rash in most cases, is considered a side effect of amoxicillin and not an allergic rash.
- In a small number of cases, the rash will be a sign of an allergic reaction which means the amoxicillin will need to be stopped.


Thank
YOU