بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | FINAL 10

Antibiotics pt.2

Done by : NST

Therapies

- **Prophylaxis: Prevention وقائي**
- **Empirical: before culture – trial-based. تجريبي**
- **Definite therapy: after confirmed diagnosis**
- **Post-treatment suppression therapy.: reduce bacterial load after treatment**

For example, in the case of recurrent UTIs, **we first treat the infection** and then continue as a **maintenance dose: Recurrent UTIs → treat → maintenance dose**. The same concept applies to viral infections such as **herpes**, where the goal is **not to cure the virus completely** but to **keep it suppressed over time: Recurrent herpes simplex → suppressive therapy.**

Therapies

We have different types of therapies regarding Antibiotics :

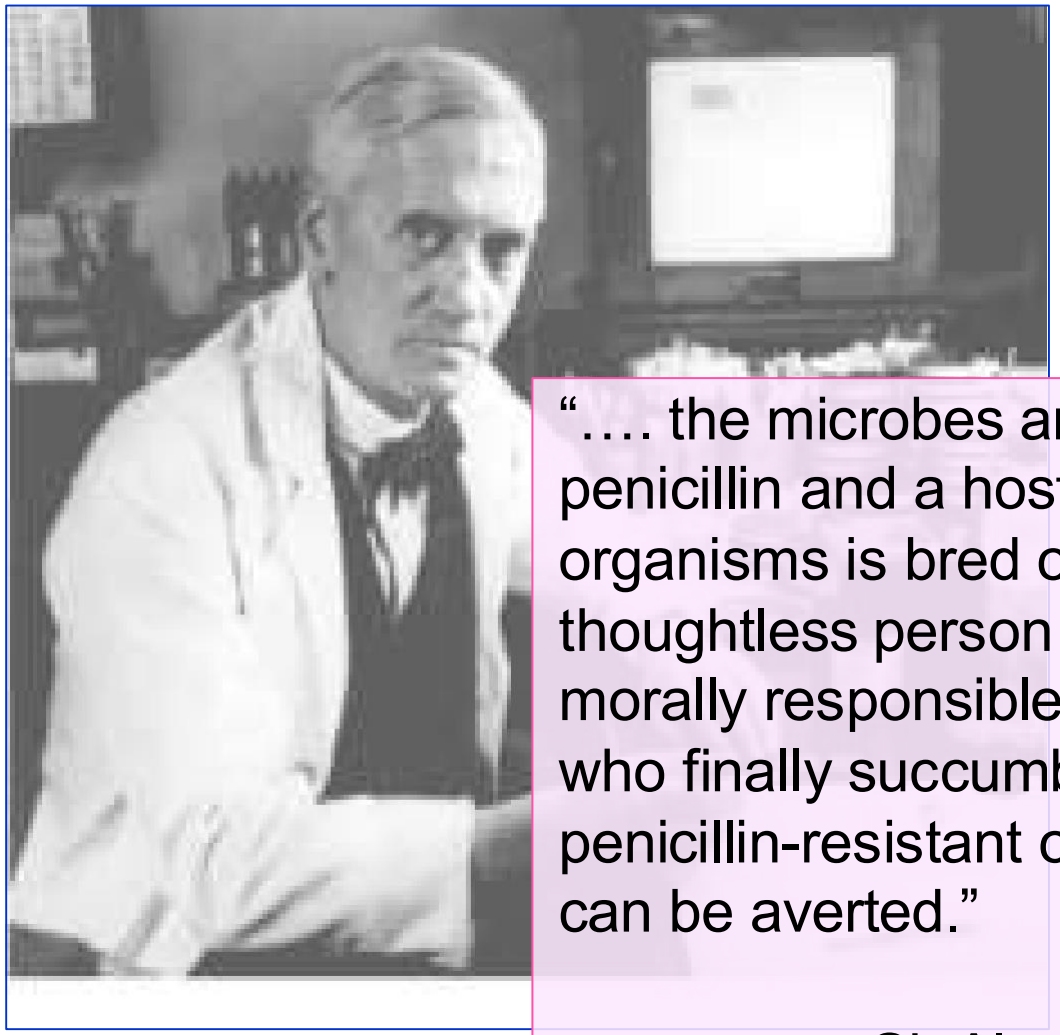
- **Prophylaxis:** In order to protect the patient from the infection, where the patient is undergoing a surgery or in the community like interaction with infectious people or when getting an injury.

- **Empirical التوقّعيّ : (the most important)** we don't know the causative microorganisms exactly, so we try to predict it, and choose the narrowest possible antibiotic.

- **Definite therapy : after** we got the **result of the culture** and **Antibiotic Susceptibility Tests (AST).**

- **Post-treatment suppression therapy :** after the treatment of a specific bacterial infection **that is suspected to reoccurrence**, we apply this type of treatment (for example UTI).

Antimicrobial Stewardship



((مِنْ أَجْلِ ذَٰلِكَ كَتَبْنَا عَلَىٰ بَنِي إِسْرَائِيلَ أَنَّهُ مَن قَتَلَ نَفْسًا بِغَيْرِ نَفْسٍ أَوْ فَسَادٍ فِي الْأَرْضِ فَكَأَنَّمَا قَتَلَ النَّاسَ جَمِيعًا وَمَنْ أَحْيَاهَا فَكَأَنَّمَا أَحْيَا النَّاسَ جَمِيعًا ۚ وَلَقَدْ جَاءَتْهُمْ رُسُلُنَا بِالْبَيِّنَاتِ ثُمَّ إِنَّ كَثِيرًا مِّنْهُم بَعْدَ ذَٰلِكَ فِي الْأَرْضِ لَمُسْرِفُونَ))

"…. the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."

- Sir Alexander Fleming, June 1945

Major influencing factors for antibiotic prescribing.
OTC: Over The Counter

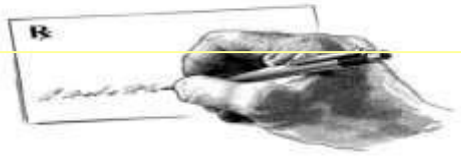
Reasons for Antibiotic Overuse :

Patient Concerns

- **Want clear explanation.**
- **Green nasal discharge.** Which is known to be sign of bacterial infection
- **Need to return to work,** the main pressure that they need to return to work as fast as they can so they will ask you to prescribe antibiotic.

Physician Concerns

- **Patient expects antibiotic.**
- **Diagnostic uncertainty.** Werther it is viral or bacterial infection.
- **Time pressure.**



Antibiotic Prescription

Barden L.S. Clin Pediatr 1998;37:665

RESISTANCE TO ANTIBIOTIC

Antibiotic	Year Deployed	Resistance Observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

Table 20.2 Microbiology: A Clinical Approach (© Garland Science)

In 1945, it was the end of WW2 and penicillin was overly used during it, As you can see using antibiotics improperly can leads to antibiotic resistance.

First bacteria developed resistance against penicillin is staphylococcus aureus because it presents on the skin and penicillin was used on wounds in WW2, which means why staphylococci is first resistant since it is most exposed to penicillin.

Whenever we are producing a new antibiotic the bacteria develop a resistance to after a while.

Bacteria developed a resistance for Cephalosporins in the same year it was introduced to the pharmacies.

Bacterial resistance mechanisms

- The spontaneous rate of mutation in bacteria is very low; about 1 in 10 million cells per division will be a mutant.

- The clinical difficulty arises when the infecting bacteria are already drug resistant.

- The four main mechanisms of resistance include:

A. Production of an enzyme that inactivates the drug
B. Mutations in the target macromolecule (Receptors)
C. Induction of mechanisms to reduce accumulation of the drug
D. Multiple drug resistance involving all these mechanisms

Antibiotic brands

These are all Antibiotics, we not are going to study or memories all of them

- 50 penicillins
- 71 cephalosporins
- 12 tetracyclines
- 8 aminoglycosides
- 1 monobactam
- 3 carbapenems
- 9 macrolides
- 3 dihydrofolate reductase inhibitors
- 1 oxazolidinone
- 30 quinolones

Common Bacteria by Site of Infection

Mouth
Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue
S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint
S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen
E. coli, Proteus
Klebsiella
Enterococcus
Bacteroides sp.

Urinary Tract
E. coli, Proteus
Klebsiella
Enterococcus
Staph saprophyticus

Upper Respiratory
S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

Lower Respiratory Community
S. pneumoniae
H. influenzae
K. pneumoniae Legionella pneumophila Mycoplasma, Chlamydia

Lower Respiratory Hospital
K. pneumoniae
P. aeruginosa
Enterobacter sp.
Serratia sp.
S. aureus

Meningitis
S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

Explanation of the previous slides Pt.1

- **Each anatomical region inside our body is having a specific bacteria that can cause its infection, which are completely different from other bacteria that cause an infection of other anatomical region (with little overlapping).**

- If you take a look at the bacteria that live and **cause infections in the** mouth:
  - ***Peptococcus, Peptostreptococcus and Actinomyces,*** they are not present at any other bacterial infection of other anatomical locations.
  - Also they all are **anaerobes.**

- If we take a look at bacteria that cause **skin infections,** we will see :
  - **Staphylococci: *staphylococcus aureus, staphylococcus epidermids, staphylococcus pyogenes.***
  - ***Pastulrealla.***

- If you examine the bacteria that cause the **bone and joint infections**, you will see a **similarity with the bacteria that causes skin infections :**

  - Similarity: ***staphylococcus aureus, staphylococcus epidermids.***
  - Not similier : ***streptococcui, gram negative rods and N.gonorrhea.***

Explanation of the previous slides Pt.2

- If you take a look at the bacteria that live and **cause infections in the abdomen and urinary tract infections you will find them Very similar to each other :**

  - **Similarity: *E. coli, Proteus, Klebsiella and Enterococcus.***

  - **Difference: only one difference :**
    - **In Abdomen: *Bacteroids species.***
    - **In Urinary tract : *staphylococcus saprophyticus.***

- When we take a I look about the bacteria that caused above a **upper respiratory tract infections** we will find them completely different from the one that caused **urinary track infection** and **abdominal track infection** with a little similarity with **community acquired lower respiratory tract infection by two bacteria : *Streptococcus pneumonia, H. Influenzae.***

  - **Bacteria that cause Upper respiratory tract infection : *Streptococcus pneumonia, H. Influenzae, Morexilla catarrhalis and Sterptoccocus pyogenes.***
  - **Bacteria that cause community aquaired lower respiratory tract infection : *Streptococcus pneumonia, H. Influenzae, Klipsella pneumoniae, Legionella pneumophila, Mycoplasma and Chlamydia.***

Explanation of the previous slides Pt.3

- There are 4 factors that affect the antibiotic that I'm going to prescribe **empirically** , which are :

1) **Site of the infection:** because there are different anatomical locations which their bacterial infections is caused by a group of limited bacteria that the prescribed antibiotic should cover.

2) **Site of acquiring the infection (Where the patient got infected) :** hospital or community.

3) **The penetration of the antibiotic :** if the patient has meningitis or bone infection, we should prescribe a highly penetrating antibiotic.

4) Whether the Antibiotic is **bactericidal or bacteriostatic :** if the patient is at :
   - life threatening situation → **prescribe bactericidal.**
   - Non-life threatening situation → **prescribe bacteriostatic.**

❖ Depending on the the 2nd factor (site of acquiring the infection), there are two types of lower respiratory tract infections :
   - **<u>Community</u> acquired lower respiratory tract infection can be caused by : *S. pneumoniae, H. influenzae, K. pneumoniae Legionella pneumophila, Mycoplasma and Chlamydia.***
   - **<u>Hospital</u> acquired lower respiratory tract infection can be caused by : *K. pneumoniae P. aeruginosa, Enterobacter sp. Serratia sp and S. aureus (merca).***

Explanation of the previous slides Pt.4

- If we take a look about the bacteria that cause **Meningitis : *S. pneumoniae, N. meningitidis, H. influenza, Group B Strep, E. coli, Listeria.***

- ✓ The antibiotic that are given to treat the **bacterial infection of the bone** or meningitis, they should be **penetrative**, and **concentrate in the bone at a concentration that is *4* times the MIC (Minimal inhibitory concentration).**

- ✓ The world guide line force you to prescribe antibiotic for a patient with bacterial infection **within 6 hours**, so we apply the **empirical treatment that cover all bacteria that can cause the infection.**
  The result of the culturing in **most cases take 3 days,** if the patient still have bacterial infection, we give them the antibiotic that was mentioned to us by the lab after applying **bacterial Identification Test & Antibiotic Susceptibility Test (AST)**, so we switch to an antibiotic that cover the bacteria recognised as the causation agent in the lap test **choosing the narrowest possible antibiotic.**

- ✓ **This switching to a narrower antibiotic (after getting the result of the culturing) is called deescalation. → Switching from Empirical to Definitive treatment.**

Dosing Matters – Penicillin Example

- Penicillin half-life is **only 30-45 minutes.**
- Retrospective review of Streptococcal infective endocarditis
  - Penicillin given **every 4 hours was associated with successful treatment vs every 6 hours (OR 2.79; 95%CI 1.43-5.62)**

Sandoe JAT, et al. J Antimicrob Chemother. 2013; June 13 [Epub ahead of print]

Antibacterial chemotherapy

- **Main Molecular Targets**

A. External integrity of the bacterial cell

1. Cell wall synthesis (Penicillins, Cephalosporins.....)

B. Protein Synthesis (Tetracyclines, Aminoglycosides, Macrolides)

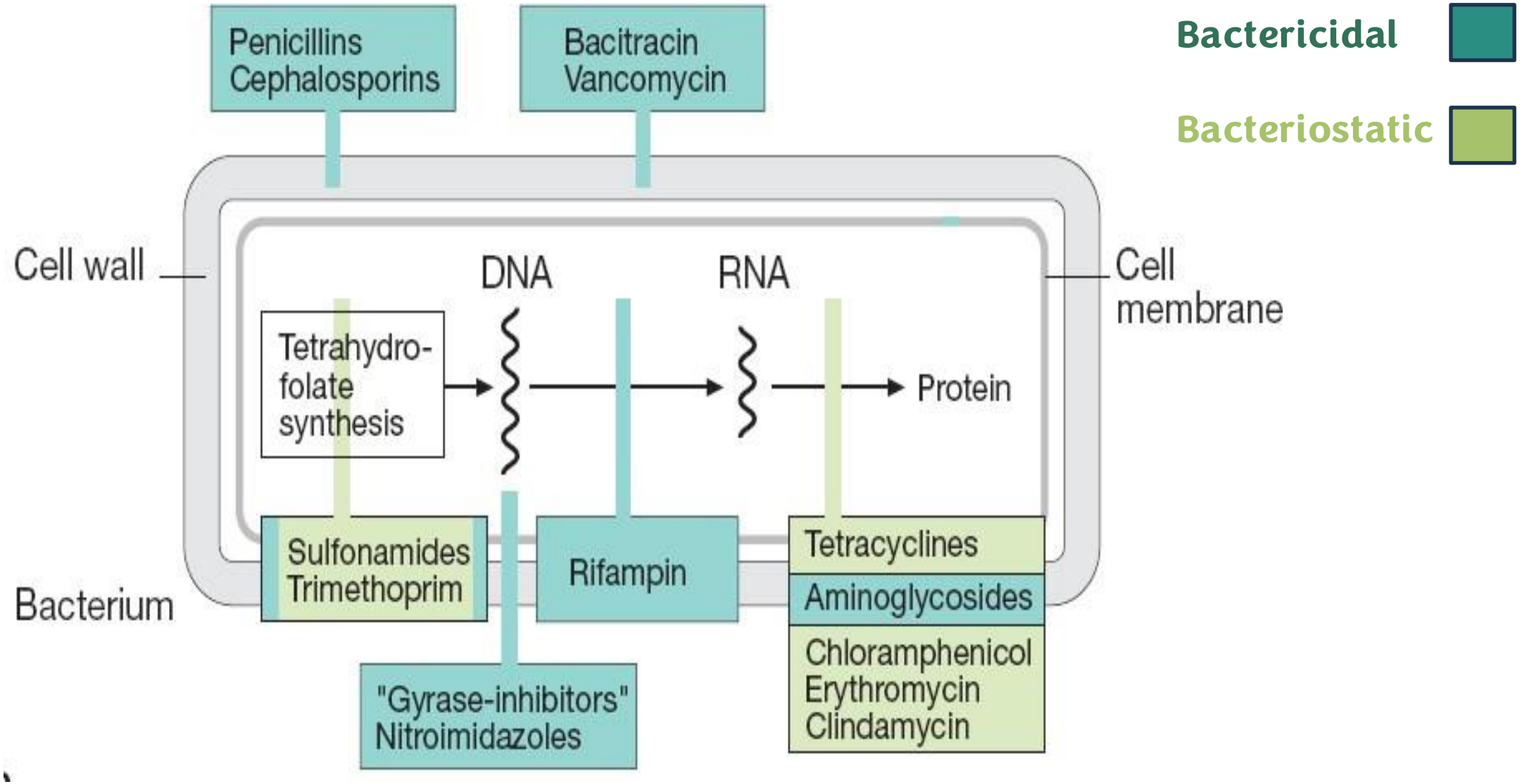
C. Perturbation of nucleic acid synthesis

1. Inhibition of the synthesis and function of folic acid (Sulphonamides, Trimethoprim)

2. Inhibition of DNA gyrase (Fluoroquinolones, Nalidixic acid)

3. Inhibition of RNA Polymerase (Rifampicin)

Main Molecular Targets



Explanation of previous figure

- **Molecular targets of antibiotics :**

1) **Attacking the cell wall, ex. :** Cephalosporins, Penicillins, Vancomycins and Bacitracin.

2) **Inhabiting Protein Synthesis :** by inhabiting the protein synthesis, they **prevent the synthesis of proteins necessary for bacterial reproduction**, which means that they work as **a bacteriostatic.**
   - ✓ Notice that there are antibiotic that contains **Aminoglycosides** which **inhabit protein synthesis,** but it is a **Bacterocidal,** because it works also on the level of the cell membrane **changing the fidelity of the plasma membrane** working as a **bactericidal.**

3) **Gyrase inhibition : Gyrase** is an enzyme that **cleaves the DNA and rebounds it again to prevent its colliding**, some **bactericidal** antibiotics work **by poisoning** this enzyme by **binding of the enzyme in the cleavable state** resulting in **cleaving of the DNA without rebounding.**

4) **Transcription inhibitors : Bactericidal , for example: Rifampin.**

(**Tetrahydro-folate** which work in purine synthesis)

5) **Tetrahydro-folate synthesis inhibition : Sulfonamides, Trimethoprim (Any one of them alone will work as a bacteriostatic, but together they give bactericidal effect).**

- ✓ **Aminoglycoside** is the most important one and the only one that still valid, **because of it's dual effect.**

Cell wall inhibitors

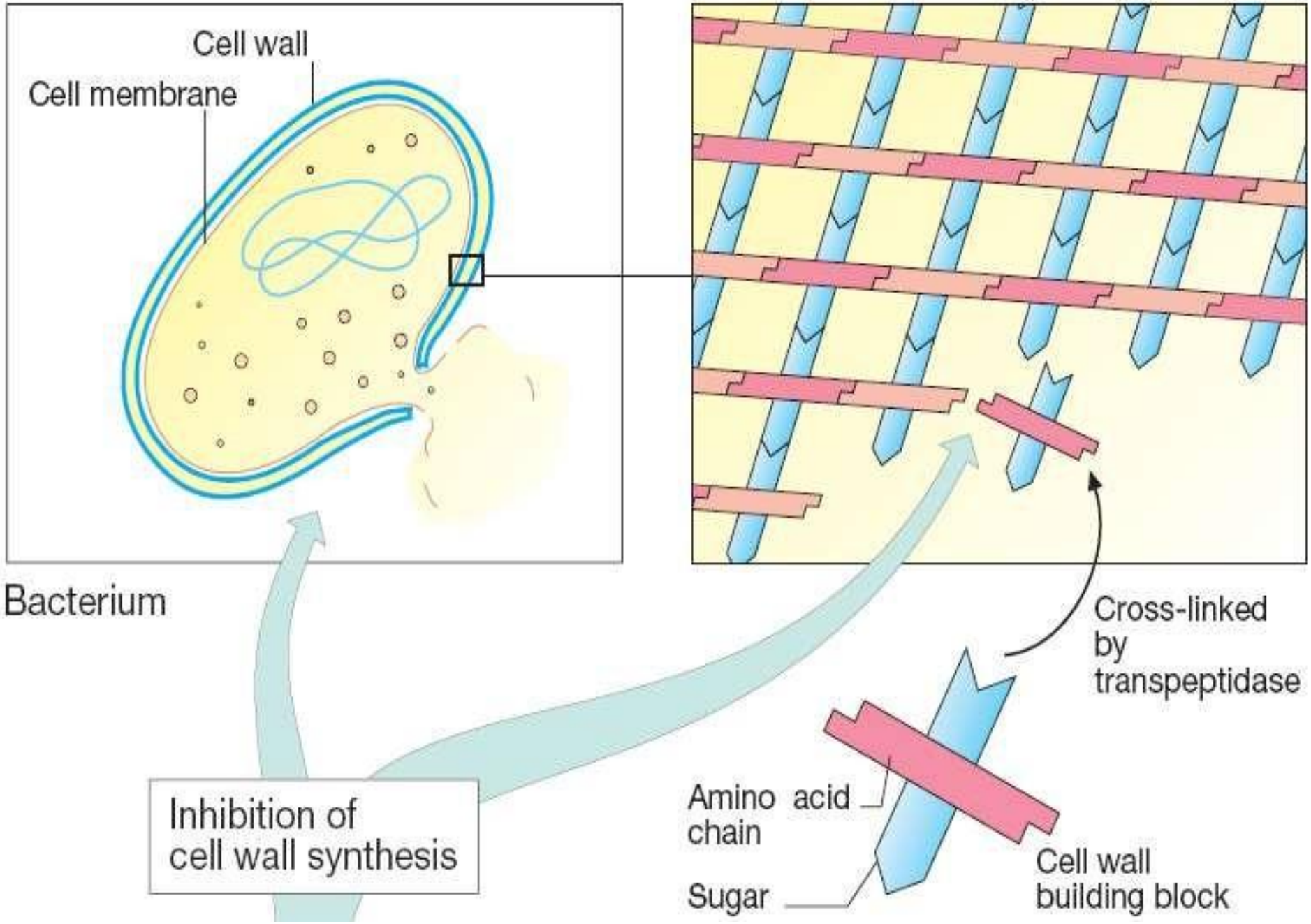
- **These agents interfere with synthesis of the bacterial cell wall (mammalians cells do not have it).**

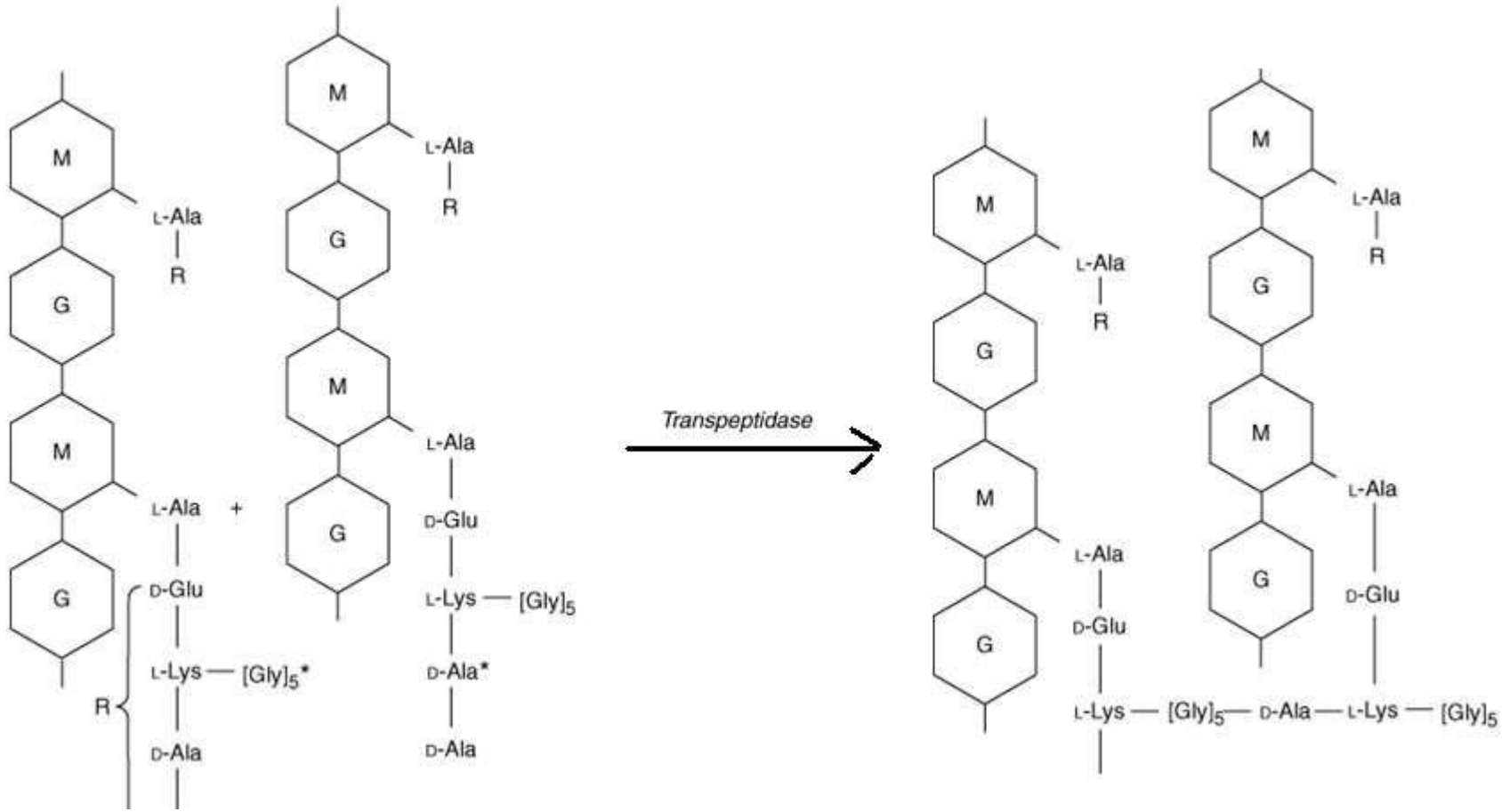
- **To be maximally effective, cell wall inhibitors require actively proliferating (multiplying) microorganism.**

- **The cell wall inhibitors include :**

  Penicillins, Cephalosporins,, Monobactams, Carbepenems,

  and Vancomycin. ……..


Cell wall
Cell membrane
Bacterium
Cross-linked by transpeptidase
Amino acid chain
Sugar
Cell wall building block
Inhibition of cell wall synthesis


M
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L-Lys — [Gly]5*
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G
M
G
L-Ala
R
L-Ala
D-Glu

The main forms of Penicillins resistance

A. b-lactamases (penicillinases) which hydrolyse the lactam ring.

b-lactamase production is particularly important in staphylococci, but they are not made by streptococci.

At least 90% of staphylococcus species in the West now produce b-lactamases.

One strategy to overcome the problem is the development of b-lactamase antagonists such as clavulanic acid which is a suicide inhibitor of the enzyme.

B. reduction in the permeability of the outer membrane in Gram-negative bacteria.

C. mutations to the penicillin-binding proteins.

Penicillins classes

- **Naturally-occurring benzylpenicillin (penicillin G) is active against some organisms but their main drawbacks are**

a. **penicillin G Sensitivity to acid hydrolysis in the stomach, which means it has to be administered by injection,**

b. **Its susceptibility to b-lactamases.**

c. **Limited activity against gram negatives.**

Natural Penicillins
(penicillin G, penicillin VK)

Broad spectrum

Mostly affect positive gram positive

Gram-positive

pen-susc *S. pneumoniae*

Group A/B/C/G strep

viridans streptococci

Enterococcus

Other

Treponema pallidum (syphilis)

Streptococcus is the kindest bacteria to medical students

Gram-negative

Neisseria sp.

Neisseria species:
Neisseria gonorrhoeae (often resistant) can't be covered by pencil in
Neisseria meningitidis (important / required)

Anaerobes

Above the diaphragm

Clostridium sp.

Any infection above the diaphragm (mouth, lung, upper respiratory tract) is more likely to involve organisms covered by penicillins

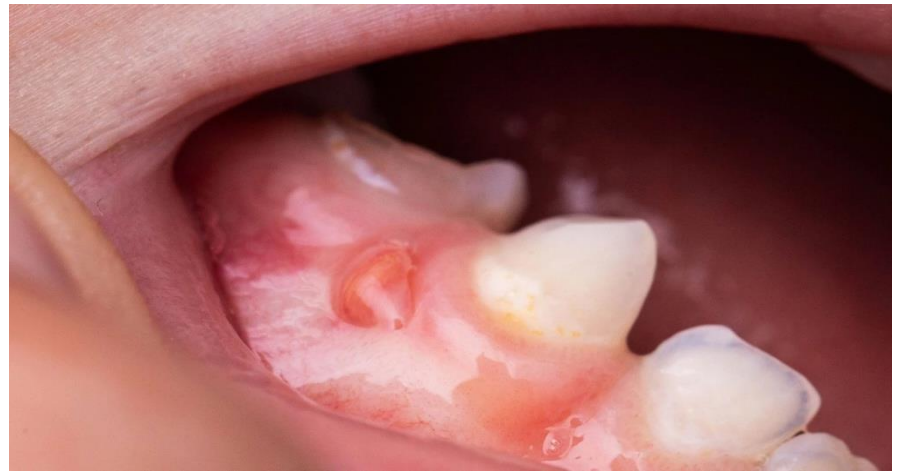
الزهري

Where is Staphylococcus?
Not covered because most Staphylococcus species produce β-lactamase, which inactivates natural penicillins.

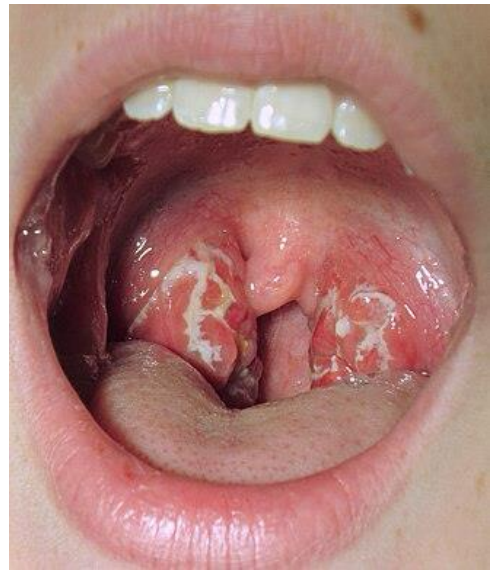
- بعد الحرب العالمية الثانية

Spectrum :
Narrow gram+|gram-
Broad gram+ and -
Extended superbug-/+/

Odontogenic infection
We chose the narowest possible
Piniciln G (IV or IM (in muscle))
I can’t give it orally it’s not acid stable so it will degregade with stomach acid
Or
Pincilin V (oral) Ospen(الاسم التجاري)
The drug that we give it empirically to odontogenic infection ?
Penicillin V or penicillin G
Most time we use it orally so we choose pencilin V



Strep throat (التهاب الحلق)
The only one in upper respiratory tract infection that can be covered empirically by penicillin



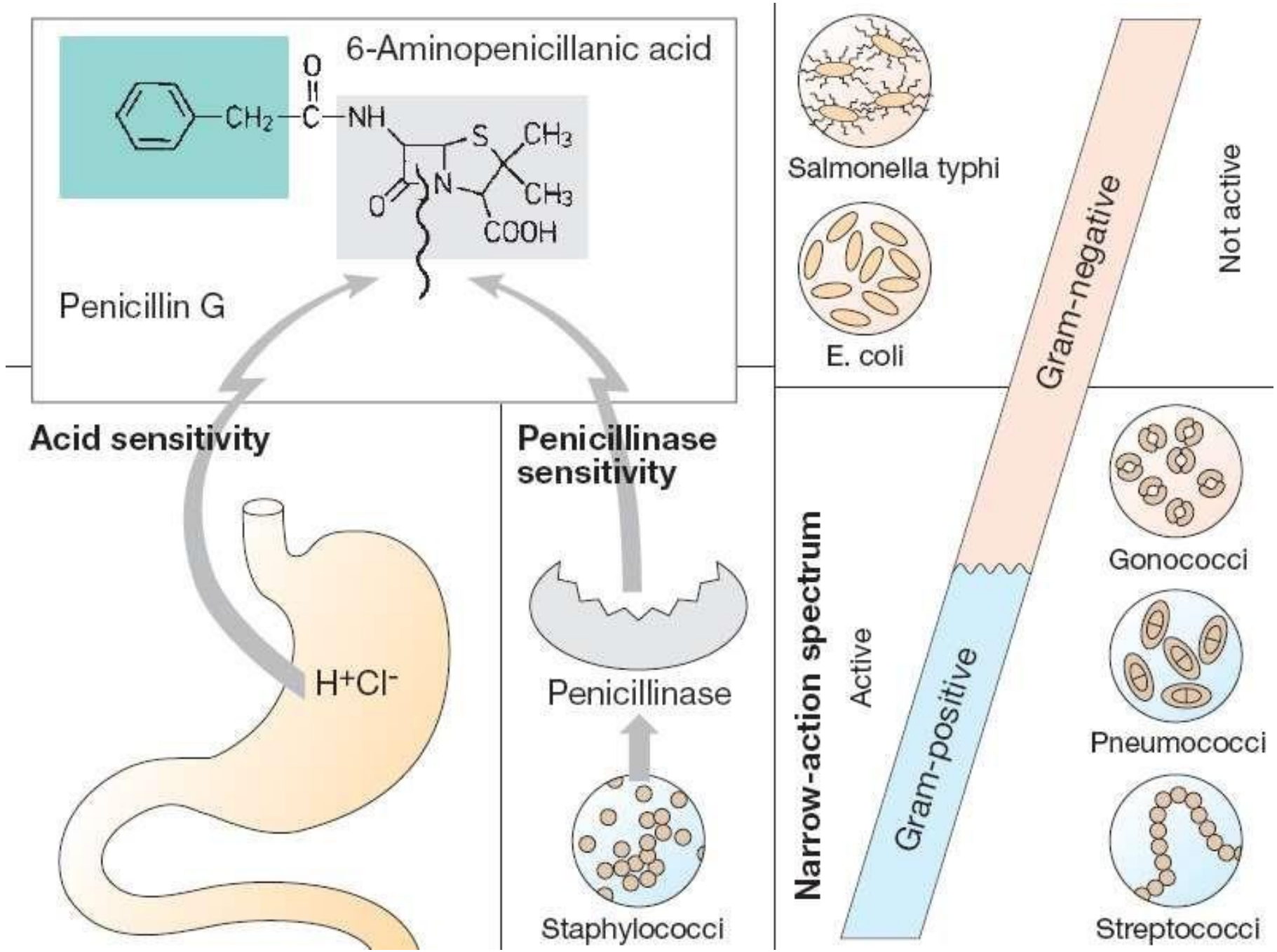
Definitive :

The lab tells you that the infection in URT from strep or other organisms from the Sam family in the slide you choose penicillin whyyy? Because you must use the Narrowest spectrum so if you gave your patient at first Augmantin you must

Change to Pencillin (de-escalation)

I can’t use as prophylactic

The problem that in mouth the infection com from both the doctor which is (staph) and the patient which is (strep+staph) so how I can protect this patient I don’t give him penicillin V or G because it doesn’t cover staph


6-Aminopenicillanic acid
Penicillin G
Acid sensitivity
Penicillinase sensitivity
H+Cl-
Penicillinase
Staphylococci
Salmonella typhi
E. coli
Gram-negative
Not active
Narrow-action spectrum
Active
Gram-positive
Gonococci
Pneumococci
Streptococci

Penicillin G clinical uses

- Streptococcal infections that include **pneumonia, otitis media, meningitis, and septic arthritis.**

- In addition, penicillin G is effective against **Neisseria meningitidis and Clostridium tetani, and Corynebacterium diphtheriae, Treponema pallidum, and Listeria monocytogenes.**

Benzathine penicillin

- Benzathine penicillin for intramuscular injection yield low but prolonged drug levels.

Strep throat

- A single intramuscular injection of benzathine penicillin, 1.2 million units, is effective treatment for beta–hemolytic streptococcal pharyngitis;
- Also prophylactic, given intramuscularly once every 3–4 weeks, it prevents re-infection..

- Reoccurrence of rheumatic fever.

- Benzathine penicillin G, 2.4 million units intramuscularly once a week for 1–3 weeks, is effective in the treatment of syphilis. Also prophylactic.

Benzathine penicillin

- **Why we have different dose in strep infection and syphilis?**

The fraction zone around each one different

Also

- **Why we have different doses ?**

Different doses are required because different organisms have different MICs.

- The higher the MIC, the lower the bacterial escape.
- يعني رفعنا ٤ مرات رح تقل فرصة البكتيريا كثيررر إنها تهرب او تتحور
- The MIC (Minimum Inhibitory Concentration) is the lowest concentration of an antibiotic that inhibits visible growth of bacteria in vitro.

رسالة من الفريق العلمي:

﴿ إِنْ أَحْسَنتُمْ أَحْسَنتُمْ لِأَنفُسِكُمْ ﴾

"If you do good, you do so for your own selves"

إحدى الآيات العجيبة التي تختزل قانونًا ربانيًا عظيمًا، والتي تعني أن الخير الذي تقدّمـــه للناس، إنما تصنعه في الحقيقة لنفسك لأنه سيرتدّ إليك، ولو بعد حين، وقد لا ترى أثره اليوم أو غدًا ولكنّه باقٍ، لا يزول، ينتظر لحظـة الحاجـة، ليأتيك كما يُرجى أو أجمل...

يَفْنَى العِبَادُ وَلَا تَفْنَى صَنَائِعُهُمْ ••• فَاخْتَرْ لِنَفْسِكَ مَا يَحْلُو بِهِ الأَثَرُ

فاختر من الأفعال أصدقها، ومن الكلمات أطيبها، فما تزرعـه في الناس، إنما تحصِدهُ في طريقك...

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			