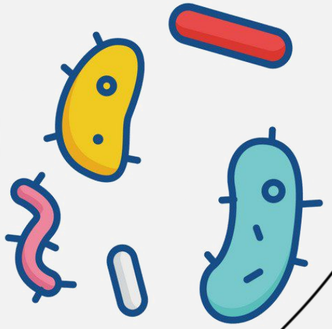
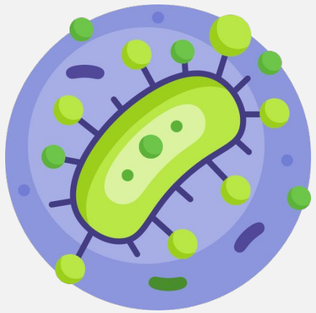
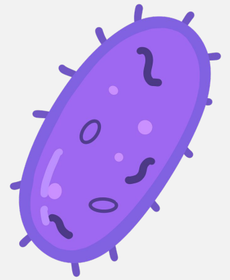






# Introduction to antibiotics

HANEEN ALRUWAILY . JOOD ALJUFAN . KHALID ALOHALI . MESHARI ALHABIB

index:

- Main text.
- **Important.**
- In boys slides only.
- In girls slides only.
- Doctors notes.
- Extra info.

# OBJECTIVES

- Define antibiotics, chemotherapy and selective toxicity
- Describe the difference between bactericidal and bacteriostatic antibiotics.
- Recognize the narrow and broad spectrum antibiotics.
- Define the therapeutic index.
- Recall the mechanism of action of antimicrobial agents.
- Recognize the various classes of antimicrobial agents(action, spectrum and side effects).
- Explain the criteria for an ideal antimicrobial.

# Antimicrobial Agents:

Note: Bacteriostatic antimicrobials don't kill microbes, the microbes are killed by the immune system.

## Antimicrobial Agents

### source

- **Chemotherapy**
  - Synthetic compounds
- **Antibiotics**
  - Natural compounds produced by microorganism. (e.g. fungi). which inhibits other microorganism

### Activity

- **Bacteriostatic**
  - Antimicrobial agent that prevents the multiplication of bacteria. (inhibits growth)
- **Bactericidal**
  - Antimicrobial agent that kills the bacteria. (better than bacteriostatic)

### Spectrum of activity

- **Narrow spectrum**
  - Antimicrobial agent that affects only selected organisms or group of bacteria (Gram -ve or +ve or anaerobes)
- **Board(Wide) spectrum**
  - Antimicrobial agent that affects both Gram +ve and Gram -ve bacteria.

# Selective Toxicity:

**Selective Toxicity** — **The ability to kill or inhibit the growth of a microorganism without harming the host cells (the more selective, the better).**

## THERAPEUTIC INDEX:

$$\text{The ratio of} = \frac{\text{Toxic dose to human}}{\text{Therapeutic dose against bacteria}}$$

444 Note: If the ratio between the toxic and therapeutic dose so big the drug becomes more safe.
If the ratio between the toxic and therapeutic dose so small the drug becomes more toxic.

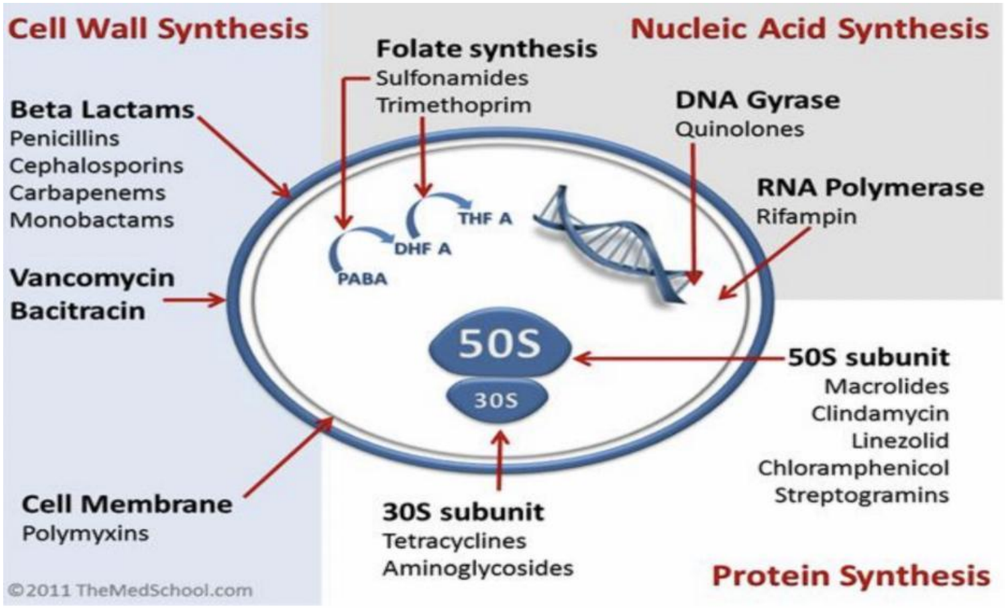
439 Explanation:
If we gave a patient 1000 mg of a specific antibiotic (which is the therapeutic dose enough to treat his infection), and the toxic does of this antibiotic (that will harm the patient) was 10000 mg
The difference is 9000 (high/ huge difference) High therapeutic index. It is safe!
if the the therapeutic dose was 1000 and the toxic dose was 1200 for example, the difference is only 200.
Then this antibiotic has a low/narrow therapeutic index. and it is NOT safe!.

Examples:
- Penicillin: has a High therapeutic index and so is safe to human.

( because it is specific it will directly target the peptidoglycan without harming the human easily )
- Aminoglycosides : has a low therapeutic index.
- Polymyxin B: has the lowest therapeutic index and very toxic to human when given systemically.

MECHANISMS OF ACTION OF ANTIMICROBIAL AGENTS

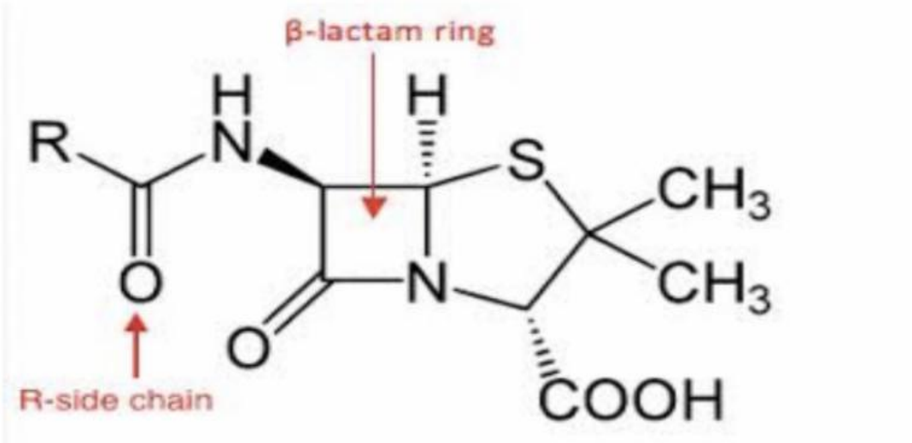
- Anti-metabolite or Competitive antagonism
  ( Stops the organism's uptake of folic acid )
- Alteration of cell membrane
- Inhibition of synthesis
  - Cell wall
    (The most important part of the bacteria)
  - Protein
  - Nucleic Acid

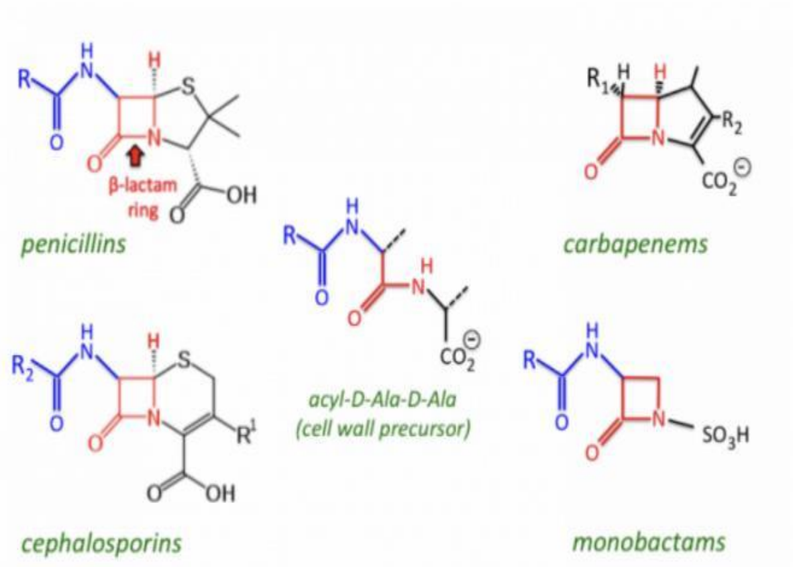


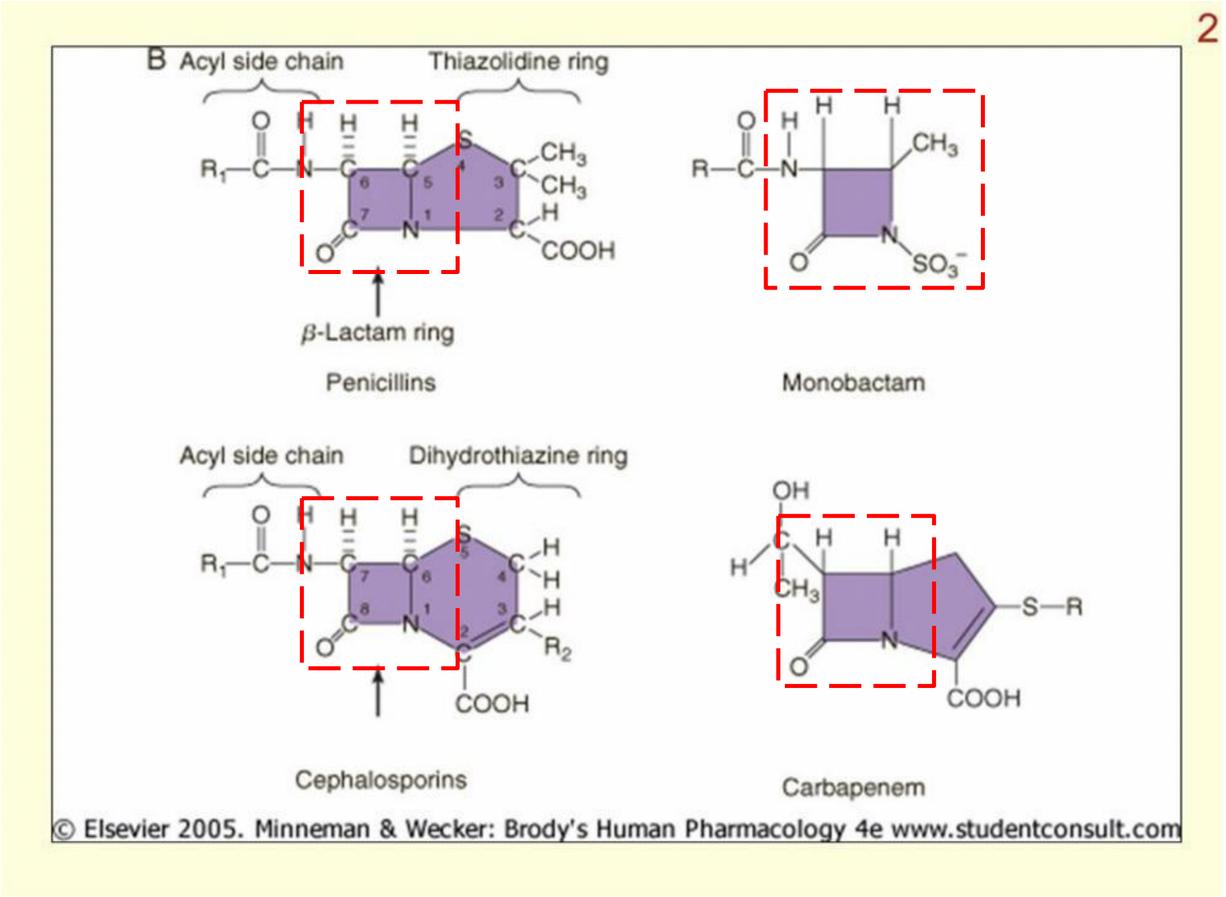
# Antimicrobials that inhibit cell wall synthesis:

| Beta - Lactam Antimicrobial Agents | Vancomycin |
|---|---|
| Both are bactericidal | |
| Composed of :<br>Beta-Lactam ring & Organic acid | Composed of:<br>Glycopeptide |
| Bind to Penicillin Binding Protein (PBP)<br>(proteins/enzymes found in the peptidoglycan, the antibiotic binds to it).<br>and interfere with trans-peptidation<br>(most important reaction that Inhibit cell wall synthesis. occurs in peptidoglycan),<br>so when the antibiotic binds and stops it, this leads to cell wall destruction. | Inhibit cell wall synthesis. |
| - Natural & Semi-synthetic<br>- Toxicity ( side effects ) : (usually it is the same for all antibiotics)<br>1. Allergy (common, mild)<br>2. Anaphylaxis (serious, life threatening).<br>3-Diarrhea.<br>4. Rash<br>- They include : ( Discussed in the next slide )<br>1. Penicillins<br>2. Cephalosporins<br>3. Carbapenems<br>4. β-Lactamase inhibitors<br>5. Monobactam (Aztreonam) | - Acts on Gram +ve bacteria only. (narrow spectrum)<br>- Given by intravenous injection (it has zero bioavailability)<br>- It is used for : (systemic infection by methicillin resistant)<br>1. MRSA (Methicillin-resistant Staph. aureus)<br>(Staph. aureus is resistant to penicillin, so we use cloxacillin, if it is also resistant to cloxacillin (MRSA), then we use vancomycin)<br>1. empirical treatment of Gram-positive infections<br>2. pseudomembranous colitis.(it is only used orally)<br>- Side effects:<br>1. Nephrotoxicity (Toxicity in kidney)<br>2. Ototoxicity (toxicity in ear)<br>3. Red man syndrome (red rash on the face, neck, upper torso)<br>4. Phlebitis ( inflammation of a vein ) |

# Beta-lactam:


β-lactam ring
R-side chain


β-lactam ring
penicillins
carbapenems
acyl-D-Ala-D-Ala
(cell wall precursor)
cephalosporins
monobactams


B Acyl side chain
Thiazolidine ring
β-Lactam ring
Penicillins
Monobactam
Acyl side chain
Dihydrothiazine ring
Cephalosporins
Carbapenem
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# Antimicrobial that inhibit cell wall synthesis: (β- Lactam Antimicrobial Agent)

| Penicillin | Cephalosporins | β- Lactamase inhibitors | Carbapenems |
|---|---|---|---|
| 1- Benzyl penicillin : Acts mainly on Gram +ve bacteria. (Because it's old)<br>E.g.<br>● Penicillin V<br>● Procaine penicillin<br>● Benzathine penicillin<br><br>2- Isoxazolyl penicillins : Effective for Staphylococcus aureus.<br>E.g.<br>● Cloxacillin. (Staph. Aureus is resistant to old penicillin because they release beta lactamase)<br><br>3- Amino-penicillins : Effective for Enterobacteria.<br>E.g.<br>• Ampicillin<br><br>4- Acyl-Aminopenicillins : Effective for pseudomonas<br>E.g.<br>● Piperacillin.<br>  | ❖ First generation: Effective on gram +ve & some Gram -ve.<br>● Cefazolin<br>● Cephalexin<br>❖ Second generation: Effective on gram +ve & some Gram -ve.<br>● Cefuroxime (-ve bacteria)<br>● Cefoxitin (Acts on Anaerobes)<br>❖ Third generation:(has expanded spectrum)Effective on gram -ve & some Gram +ve.<br>● Ceftriaxone (+ve bacteria)<br>● Ceftazidime (pseudomonas)<br>❖ Fourth generation: Effective on gram -ve & some Gram +ve<br>● Cefepime<br>❖ Fifth generation: multi-resistant Gram +ve & Gram -ve bacteria<br>● Ceftobiprole<br><br>Note:<br>as you go down from 1st generation to 4th, Gram -ve increases & Gram +ve decreases | β-Lactams but with limited antibacterial Activity<br>Irreversibly bind to β-lactamase enzyme<br><br>هو انزيم يكسر الحلقات حقت المضاد ويوقفها عن العمل. كيف نحل المشكلة؟ نضيف للمضادات Inhibitors توقف الإنزيم انه يكسر المضاد<br><br>- E.g.: Clavulanic acid, Sulbactam, & Tazobactam.<br><br>- Effective on staph. Penicillinases & broad spectrum β-lactamases.<br><br>Examples of antibiotics used with inhibitors:<br>★ Amoxicillin + Clavulanic acid.<br>(Amoxicillin has a narrow spectrum, and by adding clavulanic acid to it, becomes wide. Thus, treats more types of bacteria).<br><br>● Ticarcillin + Clavulanic acid.<br>● Piperacillin + Tazobactam. | -β-Lactams<br>★ Cover Gram +ve, Gram -ve, and anaerobes (has broad spectrum, strong).<br><br>قوية ونطاقها واسع لأنواع البكتيريا فتستعمل للمرضى الي حالتهم حادة وعندهم بكتيريا شديد المقاومة، نقلل استخدامها إلا عند الحاجة القصوى عشان مايصير في الجسم مقاومة ضدها<br><br>-Restricted to critically ill patients or patients infected with multi-resistant organisms.<br><br>-Given by injection<br><br>-Examples:<br>● Imipenem & Meropenem |

# Antibiotics that inhibit protein synthesis:

- Aminoglycosides
- Tetracyclines
- Chloramphenicol
- Oxazolidinones
- Macrolides/Lincosamides

# Antibiotic that alter the cell membrane:

## Polymyxin B and Colistin ( Polymyxin E ):

- Peptide, Active against Gram negative bacteria **only**
  (specifically aerobic or facultative anaerobe)
  (narrow spectrum)

- Bactericidal
- Used to treat multi-resistant infection caused by Gram negative bacteria such as Pseudomonas and Acinetobacter infections (used for emergencies)
- ★ High risk of nephrotoxicity
  (higher than vancomycin).

# Antimicrobial that inhibit Protein synthesis:

| Aminoglycosides<br>binds to 30s ribosomal subunit | Tetracycline<br>binds to 30s ribosomal subunit | Chloramphenicol<br>binds to 50s ribosomal subunit |
|---|---|---|
| **Bactericidal** | **Bacteriostatic** | **Bactericidal** |
| Acts only on Gram -ve bacteria (narrow spectrum) | ★ Effective for intracellular organisms<br>● Broad spectrum (Anti Gram +ve & -ve) | Broad spectrum |
| - Streptococcus & Anaerobes are naturally resistant<br><br>-E.g.:<br>● Gentamicin<br>● Amikacin<br>● Neomycin.<br><br>- Given by injection | - Effective on intracellular organisms<br>E.g. :<br>Mycoplasma, Chlamydia, Brucella.<br><br>- Also, effective on Nocardia and Vibrio cholerae.<br><br>- Classes:<br>● Short acting: tetracycline<br>● Long acting: Minocycline, Doxycycline<br>● New tetracycline: Tigecycline (Covers multi resistant Gram +ve and some Gram -ve)<br><br>- Given by Oral route.<br>★ Should NOT be used for Children under 8 years old and Pregnant woman. | - Limited use nowadays, only for severe infections NOT responding to treatment by other antimicrobials<br><br>- Can be applied topically (locally) for eye and ear infections. |
| ★ Side effects:<br><br>Nephrotoxicity & Ototoxicity<br>We use it more (in pediatrics) than colostin because its risk of nephrotoxicity is lower | Side effects:<br><br>Permanent teeth discoloration, GIT disturbance | ★ Serious side effects:<br><br>it affects bone marrow cells and cause a plastic anemia |

# Antimicrobial that inhibit Protein synthesis:

| Macrolides / Lincosamides<br>binds to 50s ribosomal subunit | Oxazolidinones<br>binds to 50s ribosomal subunit |
|---|---|
| **Bacteriostatic** | **----** |
| ● **Erythromycin ( Macrolide)**<br>● **Clindamycin ( Lincosamide)**<br><br>- Macrolides active on: Legionella, Campylobacter, Gram -ve and +ve infections for (patients allergic to Penicillins and Cephalosporins) including oral infections.<br><br>- Clindamycin acts on Staphylococci, Streptococci and anaerobes<br>Not important :<br><br>- New Macrolides :Azithromycin & Clarithromycin:<br>➔ Less side effects , better tissue penetration and longer half life | ● Linezolid.<br><br>●Inhibits protein synthesis<br><br>● Used to treat multi-resistant gram positive bacterial infections. |
| Side effects:<br>● GIT disturbance<br>★ Pseudomembranous colitis (mainly clindamycin) | Side effects:<br>● Thrombocytopenia<br><br>● Diarrhea |

# Antimicrobial that Act on nucleic Acid:

| Rifampicin | Quinolones | Metronidazole (Flagyl) |
|---|---|---|
| - Semi-synthetic, bactericidal, acts on Gram +ve bacteria and selected Gram -ve bacteria.<br><br>- Reserved for Tuberculosis (TB)<br><br>- Resistance develops quickly. Must be used in combination with other antimicrobial agent.<br><br>**Side Effects:**<br>● Causes discoloration of body fluids (You must inform the patient that their urine might change color).<br><br>● Hepatotoxicity. (Toxicity in the liver ) | - Synthetic, bactericidal, inhibit DNA Gyrase or Topoisomerase.<br><br>- Generations:<br>● First generation: Nalidixic acid-locally acting.<br><br>● Second generation: Fluoroquinolones eg. Ciprofloxacin, Norfloxacin, Ofloxacin,Levofloxacin.<br><br>● Third generation: Sparfloxacin, Gatifloxacin.<br><br>● fourth generation: Moxifloxacin, Trovafloxacin.<br><br>**Side effects:**<br>● Affects the cartilages (mainly in animals).<br>● Affects on The heart<br>★ It should be used with caution for patients under 18 year and pregnancy. | ★ A Nitroimidazole active on anaerobic bacteria and parasites.<br><br>- Causes DNA breakage.<br><br>- Used for the treatment of infections due to:<br>● Bacteroides fragilis (bacteria).<br>● Trichomonas vaginalis.<br>● amoebiasis and giardiasis (parasites). |

# Antimetabolites (folate inhibitors): Affects the metabolism of the bacteria

1. **Trimethoprim-Sulfamethoxazole (TMP-SMX).**
2. **Commonly used in Combination of TMP-SMX .**
3. **Block sequential steps in folic acid synthesis.**
4. **Effective of infections caused by different organisms, eg. Nocardia, Chlamydia, Protozoa & Pneumocystis carinii infections.**
5. **Used for the treatment of upper & lower respiratory tract infections , otitis media, sinusitis & infectious diarrhea.**
6. **Side effects: GIT, hepatitis and bone marrow depression and hypersensitivity**

**(439 Notes):**

Bacteria use folic acid in order to synthesize the nucleic acids that make up their DNA.

No folic acid = No Nucleic acid synthesis

Some bacteria can overcome the folate inhibitors by taking the folic acid from the environment

# Anti-tuberculosis agents: If the first line did not work, they use the second.

| | | Drug | Mechanism of Action | Uses | Side effects |
|---|---|---|---|---|---|
| First Line Agents | **A combination of 3 or 4 drugs used for 4-6 months.**<br><br>**For example: Patient is given INH + Rifampicin + Ethambutol + Pyrazinamide for 2 months**<br><br>**Then he continues on INH + Rifampicin for 4 months** | Isoniazid (INH) | Bactericidal<br><br>Inhibits mycolic acid synthesis. | Affects mycobacteria at different sites of lung tissues.<br><br>Used for treatment & prophylaxis of tuberculosis | 1-Peripheral neuritis (pyridoxine - vitamin B6 - added in certain patients)<br>2-hepatitis |
| | | Rifampicin (slide 11) | Bactericidal | ONLY for TB treatment | 1-Discoloration of body fluids<br>2-Hepatotoxicity |
| | | Ethambutol | Affects cell wall synthesis | TB treatment | Optic neuritis |
| | | Pyrazinamide | Exact mechanism is unknown | TB treatment | Hepatitis & arthralgia |
| Second Line Agents | **Used for resistant cases or cases that did not respond to first line drugs.** | Streptomycin | | | |
| | | Para Amino Salicylic Acid (PASA) | | | |
| | | Capreomycin | | | |
| | | Cycloserine | | | |

# Antibiotic Resistance in Bacteria:

- ❖ Resistance develops due indiscriminate use of antimicrobial agents.
- ❖ This creates a selective advantage for bacteria to grow in the presence of antibiotic.

**Types of resistance**

**Primary (Innate Resistance)**

Naturally occurring trait

E.g.:
1- Streptococcus

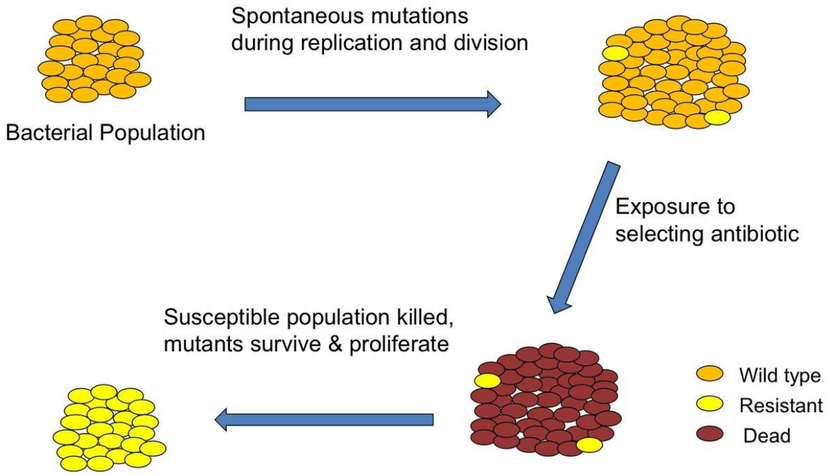
2- Anaerobes
(They are naturally resistant to Gentamicin).

**Secondary (Acquired Resistance)**

1- Mutation

2- Gene Transfer
(E.g. plasmid mediated or through transposons).

## ❖ Antimicrobial Selection of Resistance:




كل مازاد استخدام المضادات الحيوية تصير البكتيريا مقاومة أكثر، فلازم ناخذه بالطريقة الصحيحة قدر المستطاع

Note that:
Bacteria gains resistance either by mutations, by acquired genes, or by selection of resistance.

# Mechanisms of Resistance to Antimicrobial Agents:

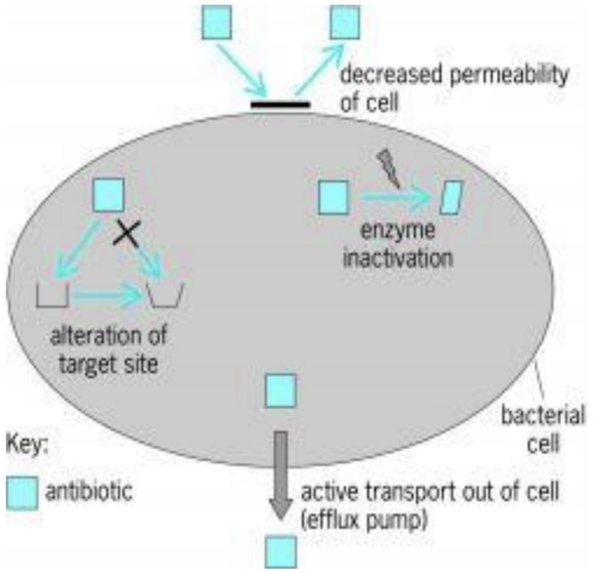
After gene transfer or mutations, how exactly will bacteria develop the resistance? By one or multiple mechanisms.

1. **Decreased permeability to antimicrobial agent**
   If the antibiotic cannot enter the bacterial cell properly, resistance will increase. E.g. (mutations that occur in the porins (channels) in gram negative bacteria).

2. **Alteration of antibiotic binding sites**
   Antibiotic is supposed to work on a specific targeted receptor, when this target changes (alter), bacteria becomes resistant.

3. **Inactivation by enzymes**
   E.g (Bacteria produces enzymes such as β-lactamase that breaks down the antibiotics).

4. **Active transport out (efflux pumps) of cells**
   Antibiotic enters the cell. However, it gets pumped out.



# Antibiotic Resistance in Bacteria, Cont.. :

## ❖ Principles of Antimicrobial Therapy

- Indication
- Choice of drug
- Route
- Dosage
- Duration
- Distribution
- Excretion
- Toxicity
- Combination use as in TB
- Prophylaxis (to prevent recurrence of infection):
    - Short term Prophylaxis:
      Meningitis
    - Long term Prophylaxis:
      Tuberculosis, Recurrent urinary tract infections , Rheumatic fever

## ❖ Criteria For Ideal Antimicrobial

- Selective toxicity.
- No hypersensitivity.
- Penetrate tissue quickly.
- Resistance not  Develop Quickly
- No effect on normal flora.
- Broad Spectrum

# Quick Summary:

1- Antimicrobial With Low Therapeutic Index Are harmful(Dangerous) and vice versa

2- Polymyxin B has the lowest Therapeutic Index.

3- Action of Antimicrobial Agent can be either Inhibition of Cell wall or Protein Synthesis or Nucleic Acid , Alterations of Cell membrane and Anti-metabolite OR competitive Antagonism.

4- Action of Antimicrobial Agent can be either Inhibition of Cell wall or Protein Synthesis or Nucleic Acid , Alterations of Cell membrane and Anti-metabolite OR competitive Antagonism.

5- Antimicrobial That inhibit Cell Wall Synthesis: β-Lactam And Vancomycin.

6- Antimicrobial That inhibit Protein Synthesis: Aminoglycosides, Tetracyclines, Chloramphenicol, Macrolides And Oxazolidinones.

7- Antimicrobial That inhibit Nucleic Acid: Rifampicin, Quinolones And Metronidazole.

**SUMMARY 439!**

**Helpful Video**

**Helpful Video**

# Take Home messages:

- Antibiotics can do harm, resistance can develop so must be used judiciously.

- Antibiotics potentiate the function of human immune system to fight microbes.

- Physicians must know the pharmacokinetics, spectrum of activity and toxicity of antimicrobial agents to make best use antibiotics.

# Quiz

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Q1: Which one of the following is a side effect of vancomycin? | | | | | | | |
| A | Teeth discoloration | B | Nephrotoxicity | C | Hepatotoxicity | D | Discoloration of body fluids |
| Q2: Example of Aminoglycosides ? | | | | | | | |
| A | Penicillin | B | Gentamicin | C | Linezolid | D | Vancomycin |
| Q3: What is a side effect of Gentamicin? | | | | | | | |
| A | Ototoxicity | B | Phototoxicity | C | Aplastic anemia | D | Teeth discoloration |
| Q4: Which antibiotic is reserved for Tuberculosis? | | | | | | | |
| A | Rifampicin | B | Isoniazid | C | Quinolone | D | Oxazolidinones |
| Q5: Which of the following is effective against staphylococcus aureus? | | | | | | | |
| A | Cloxacillin | B | Gentamicin | C | Metronidazole | D | Aminoglycosides |

1-B 2-B 3-A 4-A 5-A

# MEET THE TEAM

## Leaders

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- Abdulaziz Alanazi
- Lujain Darraj

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- AlJawharah alyahya
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