Introduction to Antibiotics

Special Thanks to Mohammed Beyari

TEAM 439
MICROBIOLOGY

VERSION 1

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.

Colour index:

- **Red: Important.**
- **Grey: Extra info & explanation.**
- **Purple: Only in girl's slides.**
- **Green: Only in boy's slides.**

Any future corrections will be in the editing file, so please check it frequently.

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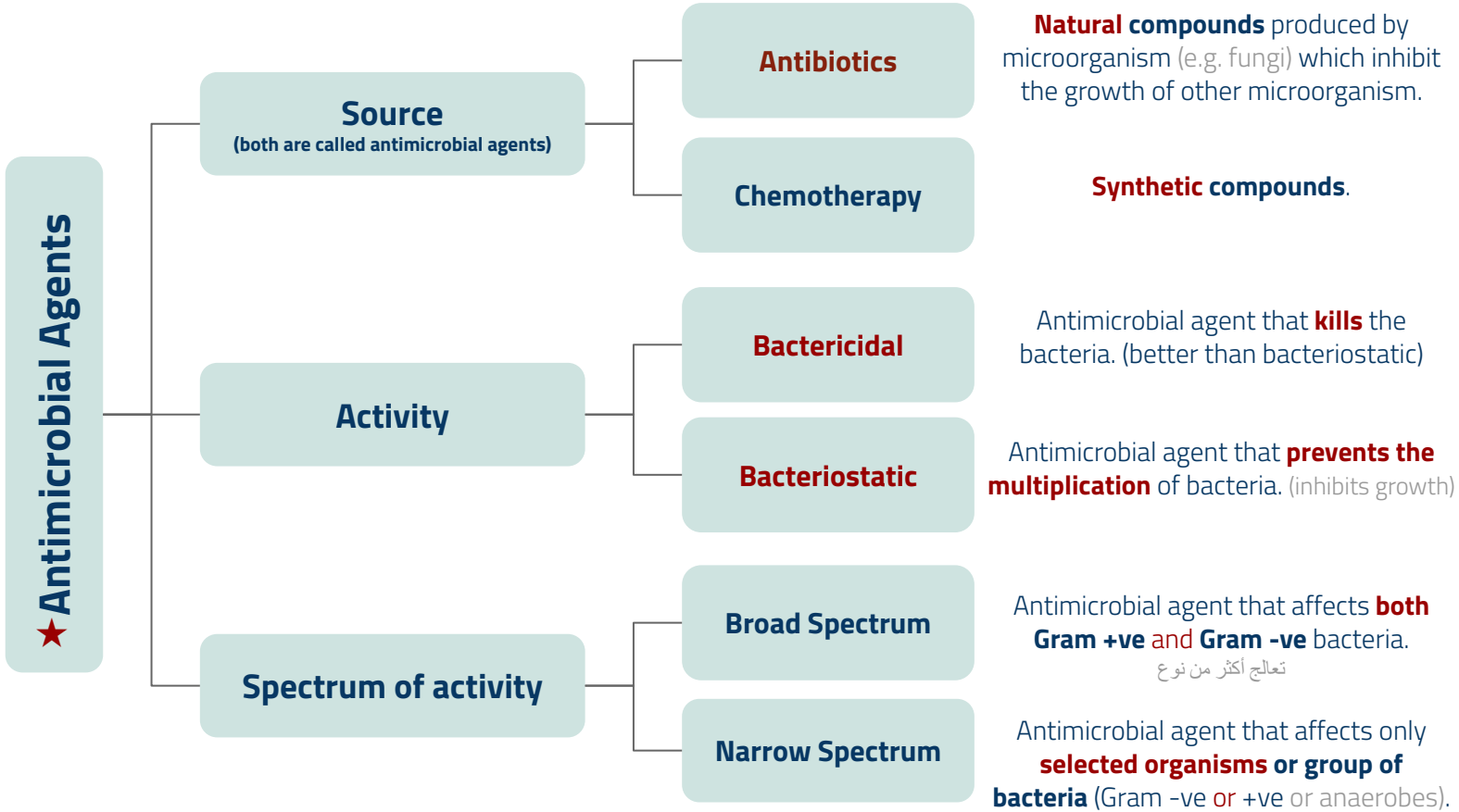


Natural compounds produced by microorganism (e.g. fungi) which inhibit the growth of other microorganism.

Synthetic compounds.

Antimicrobial agent that **kills** the bacteria. (better than bacteriostatic)

Antimicrobial agent that **prevents the multiplication** of bacteria. (inhibits growth)

Antimicrobial agent that affects **both Gram +ve** and **Gram -ve** bacteria.
تعالج أكثر من نوع

Antimicrobial agent that affects only **selected organisms or group of bacteria** (Gram -ve or +ve or anaerobes).
تعالج نوع واحد بس

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

❖ **Selective Toxicity:** (the more selective, the better)

The ability to kill or inhibit the growth of a microorganism **without harming the host cells.**

Therapeutic Index:

- The **ratio** of the $\frac{\text{Toxic dose to human.}}{\text{Therapeutic does against bacteria.}}$

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!**

BUT, 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.**

The higher the therapeutic index, the better!

❖ **Examples:**

- **Penicillin:** has a high therapeutic index and so is safe to human.

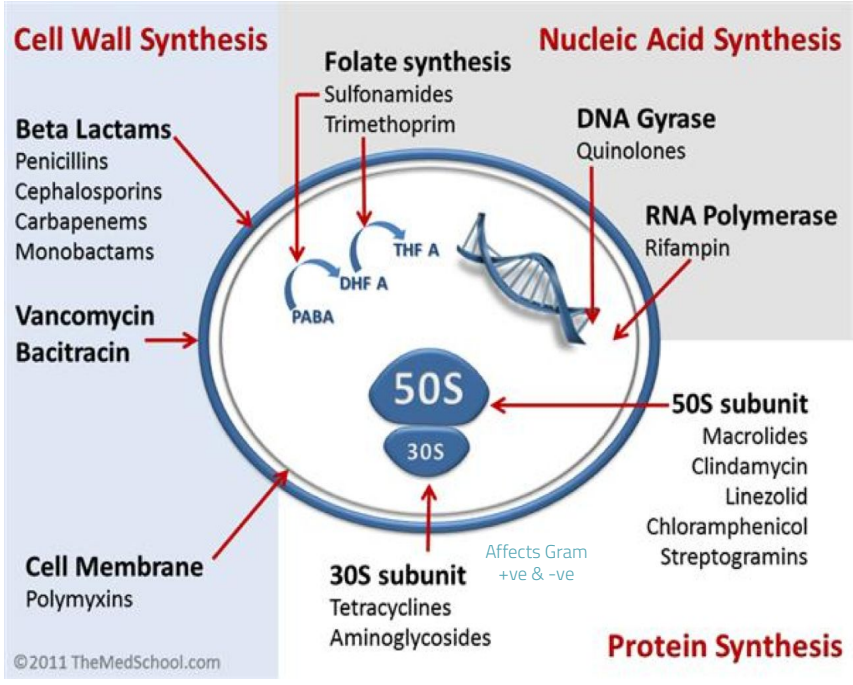
  Because it is specific and it will directly target the peptidoglycan without harming the human easily.

- **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

- Inhibition of synthesis.
  - Cell Wall (the most important part of the bacteria)
  - Protein
  - Nucleic Acid
- Alteration of cell membrane.
- Anti-metabolite or Competitive antagonism

Stops the organism's uptake of folic acid



Antimicrobials That Inhibit Cell Wall Synthesis

Beta - Lactam Antimicrobial Agents	Vancomycin
Both are **bactericidal**	
Composed of: **Beta-Lactam ring & Organic acid**	Made of: **Glycopeptide**
Bind to Penicillin Binding Protein **(PBP)** (proteins/enzymes found in the peptidoglycan, the antibiotic binds to it). and interfere with transpeptidation (most important reaction that occurs in peptidoglycan), so when the antibiotic binds and stops it, this leads to cell wall destruction.	Inhibit cell wall synthesis.
- **Natural & Semisynthetic** - **Toxicity (Side Effects):** Usually it's the same for all antibiotics 1) Allergy (common, mild) 2) Anaphylaxis (serious, life threatening) 3) Diarrhea 4) Rash - **They include:** (Discussed in the next slide) 1) Penicillins 2) Cephalosporins 3) Carbapenems 4) β-Lactamase inhibitors 5) Monobactam (Aztreonam)	- **Acts on Gram +ve bacteria only. (Narrow spectrum)** - **Given by injection only "IV".** (It has zero bioavailability) - **It is used to treat:** 1) **MRSA** (Methicillin-resistant staph. aureus). Staph.aureus is resistant to penicillin, so we use cloxacillin, if it is also resistant to cloxacillin (MRSA), then we use vancomycin. 2) **Pseudomembranous colitis** (it is only used orally to treat PMC) 3) S.epidermidis. - **Side effects:** ★ Nephrotoxicity (Kidney) 1) Ototoxicity (toxic to ear) 2) Red Man syndrome 3) Phlebitis

Penicillin

1- Benzyl Penicillin: Acts mainly on **Gram +ve** bacteria. (Because it is old).
- Penicillin V.
- Procaine penicillin.
- Benzathine penicillin.

2-Isoxazolyl Penicillins: Effective for **staphylococcus aureus**. E.g.
- ★ **Cloxacillin**. (Staph. Aureus is resistant to old penicillin because they release beta lactamase)

3-Amino-penicillins: Effective for **enterobacteria**. E.g.
- **Ampicillin**.

4- Acyl-Aminopenicillins: Effective for pseudomonas. E.g.
- Piperacillin

Cephalosporins

1-First generation: Effective on gram +ve & some Gram -ve.
- Cefazolin & Cephalexin

2-Second generation: Effective on gram +ve & some Gram -ve.
- Cefuroxime & Cephamycin (Cefoxitin; acts on anaerobes).

3-Third generation (has expanded spectrum): Effective on gram -ve & some Gram +ve.
- Ceftriaxone & Ceftazidime (pseudomonas).

4-Fourth generation: Effective on gram -ve & some Gram +ve.
- Cefepime & Cefixime.

Note: as you go down from 1st generation to 4th, Gram -ve increases & Gram +ve decreases

5-Fifth generation: multi-resistant Gram +ve & Gram -ve bacteria
- Ceftobiprole

β- Lactamase inhibitors

-β-Lactams but with limited antibacterial activity. قدرتها محدودة، تعتبر إضافة للمضاد
-Irreversibly bind to β-Lactamase enzyme.
B-Lactamase هو انزيم في البكتيريا يكسر الـ ring حق الـβ-Lactams " اللي هي المضادات" ويوقفها من العمل.
طيب كيف نحل المشكلة؟ نضيف للمضادات inhibitors توقف الإنزيم انه يكسر المضاد.

-E.g.: Clavulanic acid, Sulbactam, & Tazobactam.
-Effective on staph. Penicillinases & broad spectrum β-lactamases.

-Examples of antibiotics used with inhibitors:
- ★ **Amoxicillin + Clavulanic acid.**
- Ticarcillin+Clavulanic acid.
- Piperacillin+Tazobactam.

Amoxicillin has a narrow spectrum, and by adding clavulanic acid to it, becomes wide. Thus, treats more types of bacteria +ve/-ve/anaerobic.

Carbapenems

-β-Lactams.

★ Cover Gram +ve, Gram -ve, and anaerobes **(has broad spectrum, strong).**

-Restricted to **critically ill patients** or patients infected with **multi-resistant organisms**.
قوية وتغطي نطاق واسع من انواع البكتيريا فتستعمل للمرضى الي حالتهم حادة وعندهم بكتيريا شديدة المقاومة، ونقلل استخدامها إلا عند الحاجة القصوى عشان مايصير فيه resistance ضدها

-Given by injection.

-Examples:
- Imipenem & Meropenem.

Antibiotics That Alter Cell Membranes

- 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)

Antibiotics that inhibit protein synthesis

Remember
AT COM

- 1.Aminoglycosides
- 2.Tetracyclines
- 3.Chloramphenicol
- 4.Macrolides/ Lincosamides
- 5.Oxazolidinones

Antibiotics That Inhibit Protein Synthesis (in the ribosomes)

1.Aminoglycosides Binds to 30s ribosomal subunit	2.Tetracycline Binds to 30s ribosomal subunit
Bactericidal	Bacteriostatic
Acts only on Gram -ve bacteria (**narrow** spectrum)	★ Effective for **intracellular** organisms • broad spectrum (Anti Gram +ve & -ve)
• Streptococcus & Anaerobes are **naturally resistant.** Exampless: • **Gentamicin** • Amikacin • Neomycin. ➢ Given by injection	Effective on intracellular organisms eg. **Mycoplasma**,**Chlamydia**, Brucella. Also, effective on Nocardia and Vibrio cholerae. **Classes**: • Short acting: tetracycline • Long acting: Minocycline, Doxycycline • New tetracycline: Tigecycline (Covers multi resistant Gram +ve and some Gram -ve) ➢ Given by Oral route. ★ **Should NOT be used for Children under 8 years old and Pregnant woman**
★ **Side effects: Nephrotoxicity & Ototoxicity** We use it more (in pediatrics) than colostin because its risk of nephrotoxicity is lower	**Side effects**: Permanent teeth discoloration, GIT disturbance

3.Chloramphenicol Binds to 50s ribosomal subunit	4.Macrolides / Lincosamides Binds to 50s ribosomal subunit	5.Oxazolidinones Binds to 50s ribosomal subunit
Bactericidal	Bacteriostatic	-
broad spectrum	• Erythromycin (Macrolide) • **Clindamycin (Lincosamide)**	Anti Gram positive bacteria
➢ Limited use nowadays, only for severe infections NOT responding to treatment by other antimicrobials ➢ Can be applied **topically** (locally) for eye and ear infections. ➢ Rarely used for systemic infections	➢ Macrolides active on: *Legionella*, *Campylobacter*, Gram negative and positive infections for (patients allergic to Penicillins and Cephalosporins) including oral infections. ➢ Clindamycin acts on **Staphylococci**, **Streptococci** and **anaerobes** NOT IMPORTANT ➢ New Macrolides :Azithromycin & Clarithromycin: ➔ Less side effects , better tissue penetration and longer half life	• **Linezolid** ➢ Used to treat multi-resistant gram positive bacterial infections. ➢ Extra: used as a replacement of Vancomycin
★ **Serious side effects: it affects bone marrow cells and cause aplastic anemia**	**Side effects:** • **GIT disturbance** ★ **Pseudomembranous colitis (mainly clindamycin)**	Side effects: • Thrombocytopenia • Diarrhea

Clindamycin causes PMC by killing the intestinal flora (anaerobes) so Clostridium difficile can grow causing pseudomembranous colitis

Antimicrobials That Act on Nucleic Acid

Rifampicin
For TB

Quinolones
Nucleic acid synthesis

Metronidazole (Flagyl)
Nucleic acid synthesis

Remember:
Riyadh **Qu**ick **Metro**

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

NOTE:

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.

			Mechanism of Action	Use	Side effects
First Line Agents	A combination of 3 or 4 drugs used for 4-6 months. For example: Patient is given INH + Rifampicin+ Ethambutol + Pyrazinamide **for 2 months** Then he continues on INH + Rifampicin **for 4 months**	Isoniazid (NH)	Bactericidal Inhibits mycolic acid synthesis.	Affects mycobacteria at arthralgia. Used for treatment & prophylaxis of TB	1-Peripheral neuritis (pyridoxine - vitamin B6 - added in certain patients) 2-hepatitis.
		Rifampicin	Bactericidal Go back to Slide 11	ONLY for TB treatment	Discoloration of body fluids 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 aminosalicylic 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).

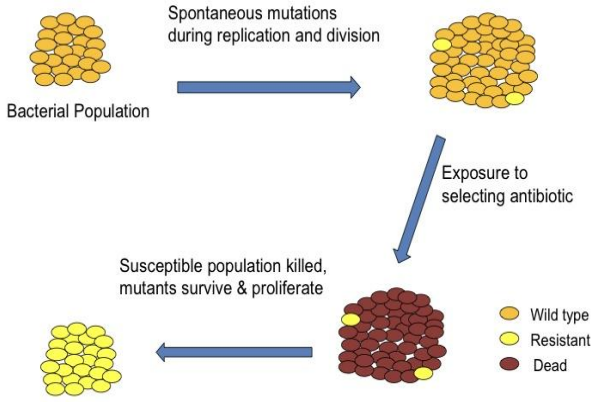
اخذنا بأول محاضرة كيف تنتقل الجينات بالبكتيريا، وعن طريق الـ**conjugation** كان R plasmid ينقل خاصية مقاومة المضادات الحيوية

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

Antimicrobial Selection of Resistance

كل ما زاد استخدام المضادات الحيوية تصير البكتيريا مقاومة أكثر، ولازم تستعمل بطريقة صحيحة قدر المستطاع

Example: patient had infection.
1- Due to mutations, had a some resistant bacteria (yellow).
2- Took antibiotic, all bacteria die (red) **except** the resistant ones.
3- Resistant bacteria begin to reproduce.



Mechanisms of Resistance to Antimicrobial Agents.

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

1

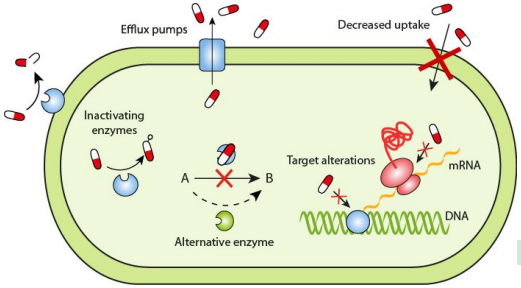
Decreased permeability to antimicrobial agent*

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.

Example: **Staphylococcus Aureus**

- Before, it was always affected by penicillin. Now, it is resistant due to enzymatic inactivation of the antibiotic by the enzyme "beta lactamase".
صار عندها إنزيم بيتا لاكتاميز اللي بيكسر ويخرب المضاد.

- Also, we cannot use cloxacillin on some staph. Aureas, because it changed the binding site (target or receptor) that antibiotics (β-lactams) bind to.
غيرت الريسبترز حقتها، فصارت بيتا لاكتامز (المضادات) ما تشبك عليها.

Antibiotic Resistance in Bacteria, contd..

❖ 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)

1- Short term prophylaxis:

- Meningitis.

2- Long term prophylaxis:

- Tuberculosis.
- Recurrent urinary tract infections.
- Rheumatic fever.

❖ Criteria For Ideal Antimicrobial

- Selective toxicity.
- No hypersensitivity.
- Penetrate tissue quickly.
- No quick development of resistance.
- No effect on normal flora.
- Broad.

Notes

- β-lactams (including penicillin, cephalosporins, β-lactamase inhibitors, and carbapenems) & Vancomycin all work on cell wall.

- β- Lactamase inhibitors are β- Lactams with limited abilities, its is added to antibiotic with narrow spectrum, to make it stronger (broad spectrum). The way it works is that it irreversibly binds to β-Lactamase (enzyme) and shuts it off so it cannot affect the antibiotic.

- In cephalosporins, as you go down from first generation to fourth, Gram -ve increases and Gram +ve decreases. However, fifth is special (it is synthetic, affects both +ve/-ve).

- Bacteria will gain resistance in **three ways**: mutations, gene transfer, or selection. This will lead to using one or multiple **mechanisms** to break down antibiotics.

★Summary

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MCQs

1- Measurement of antibiotic safety.
A- Selective toxicity.
B- Bacteriostatic.
C- Therapeutic index.
D- Aminoglycosides.

2- The antibiotic that affects bone marrow and may cause aplastic anemia is:
A- Oxazolidinones
B- Lincosamides
C- Chloramphenicol
D- Tetracycline

3- The most common antibiotic that affects on liver and cause hepatotoxicity.
A- Metronidazole.
B- Monobactam.
C- Rifampicin.
D- Carbapenems.

4- Which of the following is correct about Aminoglycosides?
A- Bactericidal, Anti-Gram positive
B- Bactericidal, Anti-Gram negative
C-Bacteriostatic, Anti-Gram positive
D-Bacteriostatic, Anti-Gram negative

5-Which of the following antibiotics should NOT be used for Children under 8 years old?
A-Colistin
B- Penicillin
C- Carbapenem
D-Tetracycline

6- Bacteria do not develop resistance by:
A- Natural traits.
B- Mutations
C- Gene transfer
D- Selection

6-A
5-D
4-B
3-C
2-C
1-C

MCQs

7- Cloxacillin is an example of:
A- Benzyl penicillin.
B- Aminopenicillin.
C- Acyl-aminopenicillins.
D-Isoxazolyl penicillins.

8- What is true about carbapenems is:
A- Cover gram +ve only
B- Given orally
C- Has a broad spectrum
D- Has a narrow spectrum

9- The most harmful antibiotics is?
A- Antibiotic with therapeutic index of 9000
B- Antibiotic with therapeutic index of 2000
C- Antibiotic with therapeutic index of 7000
D- Antibiotic with therapeutic index of 5000

SAQ

1- What are the 4 mechanisms of resistance to antimicrobial agents?

Slide 15

2- What is selective toxicity?

Slide 4

4- How is the therapeutic index measured? What does a high or low index indicates regarding the safety?

Slide 4

9- B
8- C
7- D

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