Microbiology Team
Med441

Introduction to Antibiotics

MED441
KING SAUD UNIVERSITY

Revised & Reviewed by: Abdulaziz & Bahammam Faye Wael Sendi

Microbiology Team441

Editing file

Color Index:

- Main text
- Boys slides only
- Girls slides only
- Doctor's notes
- Extra information
- ***Important***

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.
- Discuss mechanisms of resistance to antibiotics.

Definitions/Terminologies

Helpful video

Antimicrobial agents

01 Antibiotic:
Natural compounds produced by microorganism which inhibit the growth of other microorganism

02 Chemotherapy:
Synthetic (مصنّعة في المختبر) compounds

Activity

03 Bacteri*cidal*:
Antimicrobial agent that kills the bacteria. (better than bacteriostatic)

04 Bacterio*static*:
Antimicrobial agent that prevents the multiplication of bacteria. (inhibits growth)

Spectrum of Activity

05 Broad Spectrum:
Antimicrobial agent that affects both Gram +ve and Gram -ve bacteria.

06 Narrow Spectrum:
Antimicrobial agent that affects only selected organisms or group of bacteria (Gram -ve or +ve)

07 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 $\frac{\text{Toxic dose to human}}{\text{Therapeutic does against bacteria}}$

★ **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.

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!

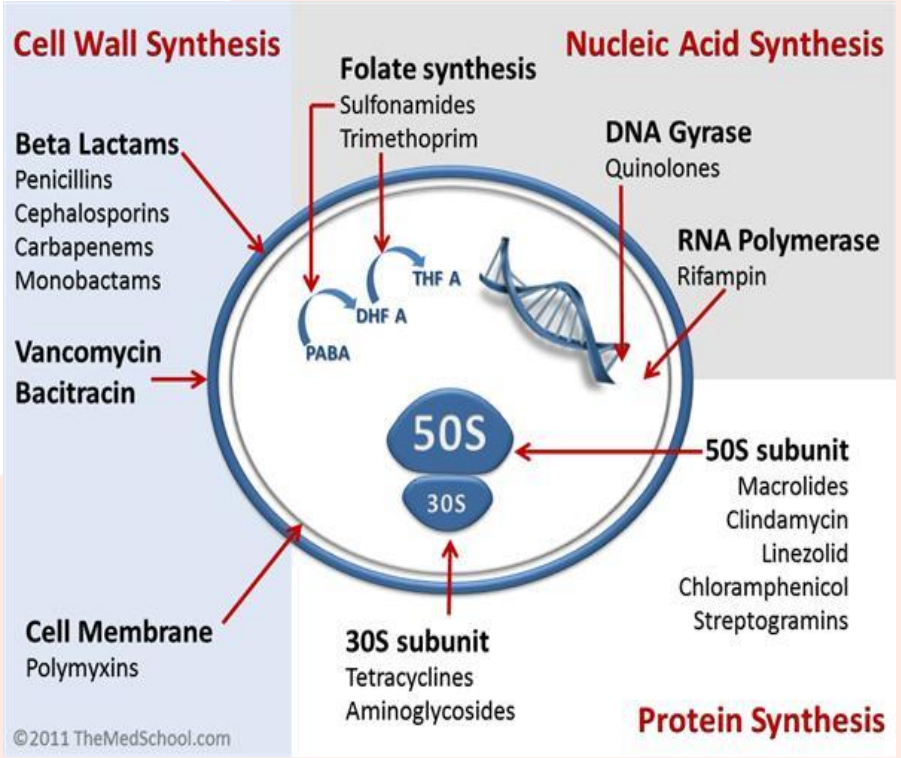
BUT, if the the therapeutic dose was 1000 and the toxic dose was 1200 for example, the difference is only 200. Then this antibiotic has a low/narrow therapeutic index and it is NOT safe.

The higher the therapeutic index, the better!

Mechanisms of action of antimicrobial agents

Helpful video

1. Inhibition of Synthesis
   a) Cell Wall
   b) Protein
   c) Nucleic Acid
2. Alteration of cell membrane
3. Anti-metabolite or Competitive antagonism



Antibiotics 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):** 1) Allergy (common, mild) 2) Anaphylaxis (serious/life threatening like trouble swallowing/breathing) 3) Diarrhea • **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 staphylococcus aureus). Staphylococcus 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) Staphylococcus epidermidis. • **Side effects:** ★ ***Nephrotoxicity*** (Toxicity in kidneys) 1) ***Ototoxicity*** (toxicity in hearing) 2) ***Red Man syndrome*** 3) Phlebitis

Beta - Lactam Antimicrobial Agents

Penicillins

1.Benzyl Penicillin:
- Acts mainly on ***Gram +ve*** bacteria
- e.g.: Penicillin V, Procaine penicillin, & Benzathine penicillin

2.Isoxazolyl Penicillin:
- Effective for **staphylococcus** aureus
- e.g.: ***Cloxacillin***

3.Amino-penicillins:
- Effective for Enterobacteria
- e.g.: ***Ampicillin*** (acts on Gram +ve, -ve, & ***anaerobes***)

4.Acyl Aminopenicillin:
- Effective for ***Pseudomonas***
- e.g.: ***Piperacillin*** & Mezlocillin

Cephalosporins

1.First generation: Gram +ve and some Gram -ve
- ***Cefazolin***
- Ceohalexine

2.Second generation: Gram +ve and some Gram -ve
- Cefuroxime (for Gram -ve)
- Cefoxitin (acts on ***anaerobes***)

3.Third generation (expanded spectrum): Gram -ve and some Gram +ve
- ***Ceftriaxone***
- Ceftazidime (pseudomonas)

4.Fourth generation: Gram -ve and some Gram +ve
- ***Cefepime***

5.Fifth generation: multi-resistant Gram +ve and Gram -ve bacteria
- ***Ceftobiprole***

Beta - Lactam Antimicrobial Agents, cont..

β-Lactamase Inhibitors

- β-Lactams with limited antibacterial activity. (added to antibiotics)
- ***Irreversibly bind to β-Lactamase enzyme.***
- Examples: ***Clavulanic acid,*** Sulbactam***, & Tazobactam.***
- Effective on staph. Penicillinases & ***broad spectrum β-lactamases.***
- Examples of antibiotics used with inhibitors:
  1. Amoxicillin+***Clavulanic acid***
  2. Ticarcillin+Clavulanic acid
  3. Piperacillin+***Tazobactam***

- β-Lactamase is an enzyme in bacteria that breaks β-lactam rings in antibiotics (like penicillin). β-lactamase inhibitors are used to inhibit this enzyme, and allows antibiotics with β-lactam rings to work on bacteria.

Carbapenems

- β-Lactams.
- Cover ***Gram +ve, -ve & anaerobes (broad spectrum)***
- Restricted to critically ill patients or patients infected with ***multi-resistant organisms.***

(439 noteقوية وتغطي نطاق واسع من أنواع البكتيريا فتستعمل للمرضى الي حالتهم حادة وعندهم بكتيريا شديدة المقاومة، ويكون استخدامها عند الحاجة القصوى عشان ما يصير فيه مقاومة ضدها

- Given by injection.
- Ex: Imipenem & Meropenem

Antibiotics that alter cell membranes

Polymyxin B and Colistin (Polymyxin E):

★ Peptide, Active against Gram ***negative*** bacteria only (***narrow spectrum***)

★**Bacteri*cidal***

★ Used to treat multi-resistant infection caused by Gram negative bacteria.
★ such as Pseudomonas and Acinetobacter infections (used for emergencies)

★ High risk of ***nephrotoxicity*** (Therapeutic index very low)

Antibiotics that inhibit protein synthesis

Aminoglycosides (Therapeutic index very low)	**Tetracyclines**
Binds 30s ribosomal subunit	
Bacteri***cidal***	Bacterio***static***
Acts only on Gram ***-ve (narrow spectrum)***	Acts on Gram ***-ve and +ve (broad spectrum)***
• **Examples: *Gentamicin,*** Amikacin, Neomycin • Streptococci + Anaerobes are naturally ***resistant*** • Given mainly by ***injection***	**Classes:** 1. Short acting: ***Tetracycline*** 2. Long acting: Minocycline ***, Doxycycline*** (good CSF penetration). 3. New tetracycline : ***Tigecycline*** (covers multiresistant Gram positive and some Gram negative bacteria and ***anaerobes***). • Given by oral route. • Effective for Intracellular organisms eg. Mycoplasma, Chlamydia ,Brucella also effective for Nocardia and Vibrio. ***Should NOT be used for children < 8 year old and pregnant women.***
Side effects: • dose related ***Nephrotoxicity*** (toxicity in the kidneys) and ***Ototoxicity*** (toxicity in the ears)	**Side effects:** • ***Permanent teeth discoloration*** • GIT disturbance

Antibiotics that inhibit protein synthesis

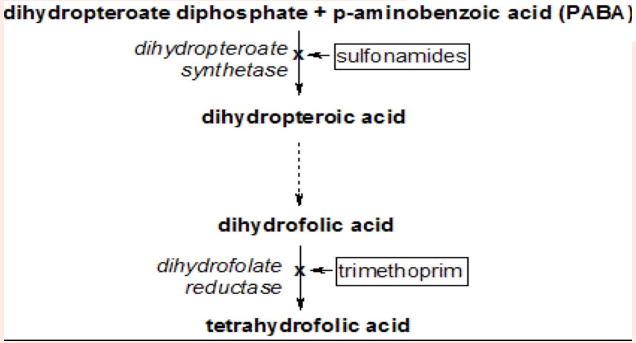
Chloramphenicol	Macrolides/Lincosamides	Oxazolidinones
Binds 50s ribosomal subunit		
Bacteri***cidal***	Both are Bacterio***static***	——
Acts on Gram -ve and +ve ***(broad spectrum)***	• Erythromycin→ Macrolide • ***Clindamycin***—>Lincosamide • Macrolides active on: Legionella, Camylobacter, ***Gram negative and positive*** infections for patients allergic to Penicillins and Cephalosporins, including oral infections.New Macrolides: Azithromycin & Clarithromycin. (Less side effects , better tissue penetration and longer half life) • Clindamycin (Lincosamide) acts on Staphylococci, Streptococci and ***anaerobes***	Acts on Multiresistant ***Gram +ve***
• ***Limited use*** nowadays: only for severe infections not responding to treatment by other antimicrobials. (Because of the toxicity of it) • Can be applied ***topically*** (locally) for eye and ear infections.		Example ; Linezold
Side effects: • ***bone marrow cells*** • ***aplastic anemia.***	Side effects : • GIT disturbance • ***Pseudomembranous colitis (mainly clindamycin).***	Side effects: • Thrombocytopenia • Diarrhea

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

Antimicrobials that act on nucleic acids (439mnemonic: Riyadh Quick Metro)

Rifampicin	Quinolone	Metronidazole
Bactericidal	Bactericidal	——
Semi-synthetic	Synthetic	——
• Acts on ***Gram +ve*** and ***selected Gram -ve*** bacteria. • Reserved for ***Tuberculosis*** • Resistance develops quickly (if used alone) so it must be taken in combination with other antimicrobial agent.	• Generations: ➢ First generation: *Nalidixic acid*–locally acting. ➢ Second generation: *Fluoroquinolones* eg. Ciprofloxacin, Norfloxacin, Ofloxacin,Levofloxacin. ➢ Third generation: *Sparfloxacin*, *Gatifloxacin* ➢ Fourth generation: *Moxifloxacin*, *Trovafloxacin* • ***Should be used with caution for patients under 18 year and pregnancy.*** • Inhibits DNA Gyrase and /or Topoisomerase.	• 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).
Side effects: Causes *discoloration of body fluids and hepatotoxicity* (toxicity in the liver)	Side effects: Affects the ***cartilages*** (mainly in animals) and the ***heart***.	——

Antimetabolites (folate inhibitors)



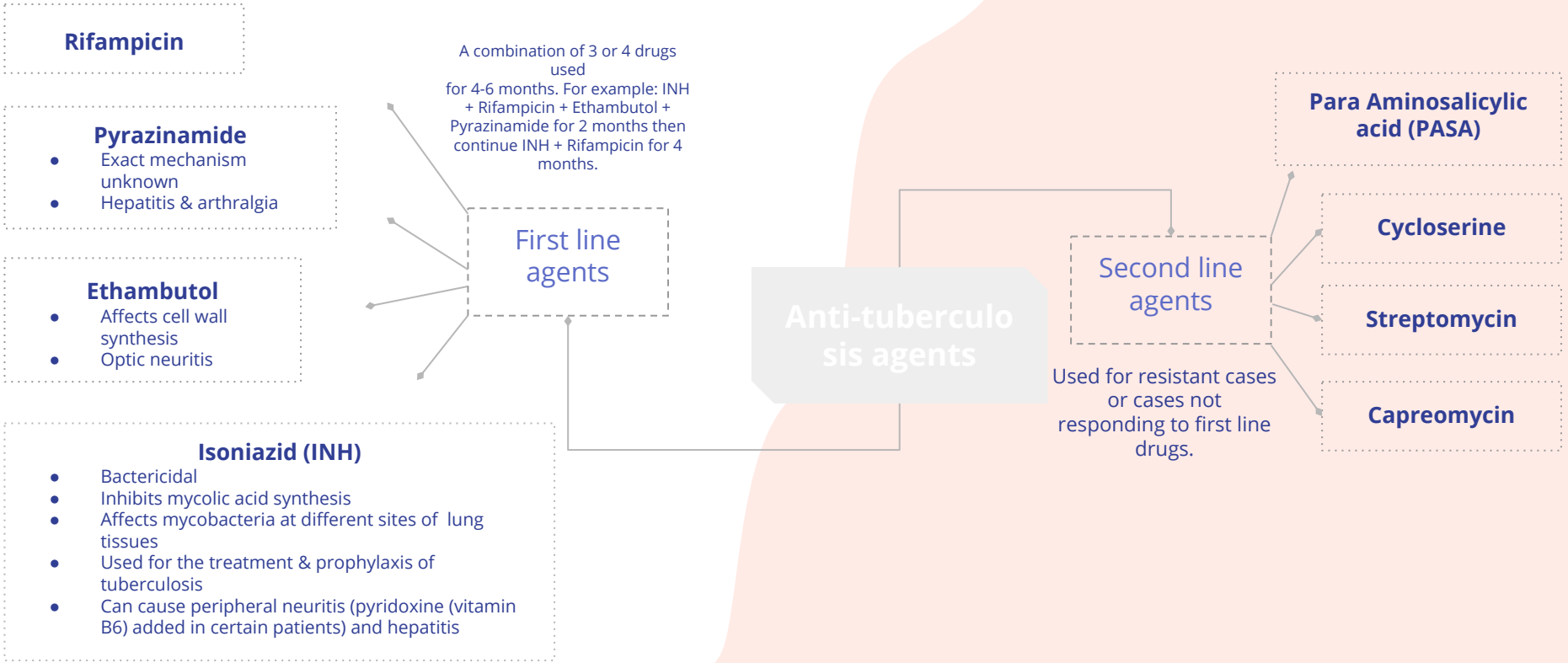
- Trimethoprim-Sulfamethoxazole (TMP-SMX)
- Commonly used in Combination of TMP-SMX.
- Block sequential steps in ***folic acid synthesis.***
- Effective of infections caused by Gram positive, negative bacteria, and different organisms such as: ***Nocardia, Chlamydia, Protozoa & Pneumocystis carinii infections.***
- Used for the treatment of upper & lower respiratory tract infections, otitis media, sinusitis & infectious diarrhea.
- Side effects: ***GIT, hepatitis, bone marrow depression*** (when the number of WBCs, RBCs, and platelets in your body decrease) ***& hypersensitivity.***

(439note) 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



Antibiotic Resistance in Bacteria

عشواني
Resistance develops due to indiscriminate use of antimicrobial agents, this creates a selective advantage for bacteria to grow in the presence of antibiotic.

Types Of Resistance:

1 **Primary (Innate) resistance** طبيعي

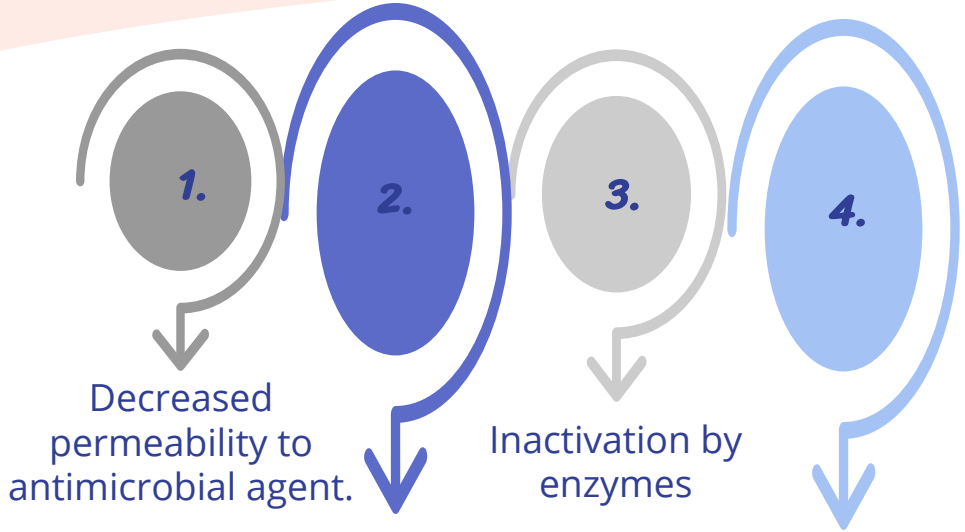
eg. Streptococcus & anaerobes are naturally resistant to Gentamicin.

2 **Secondary (acquired) resistance** مكتسب

Due to :
- ***Mutation***
-***Gene transfer*** (e.g. plasmid mediated (conjugation) or through transposons)

Mechanisms of Resistance to Antimicrobial Agents

How does the bacteria protect itself from antibodies ?

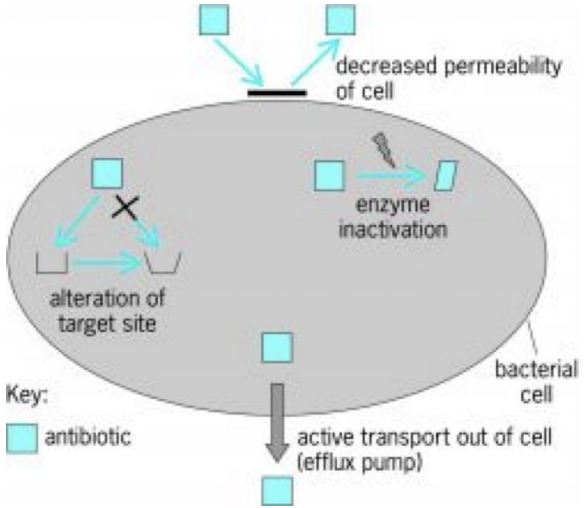


Decreased permeability to antimicrobial agent.

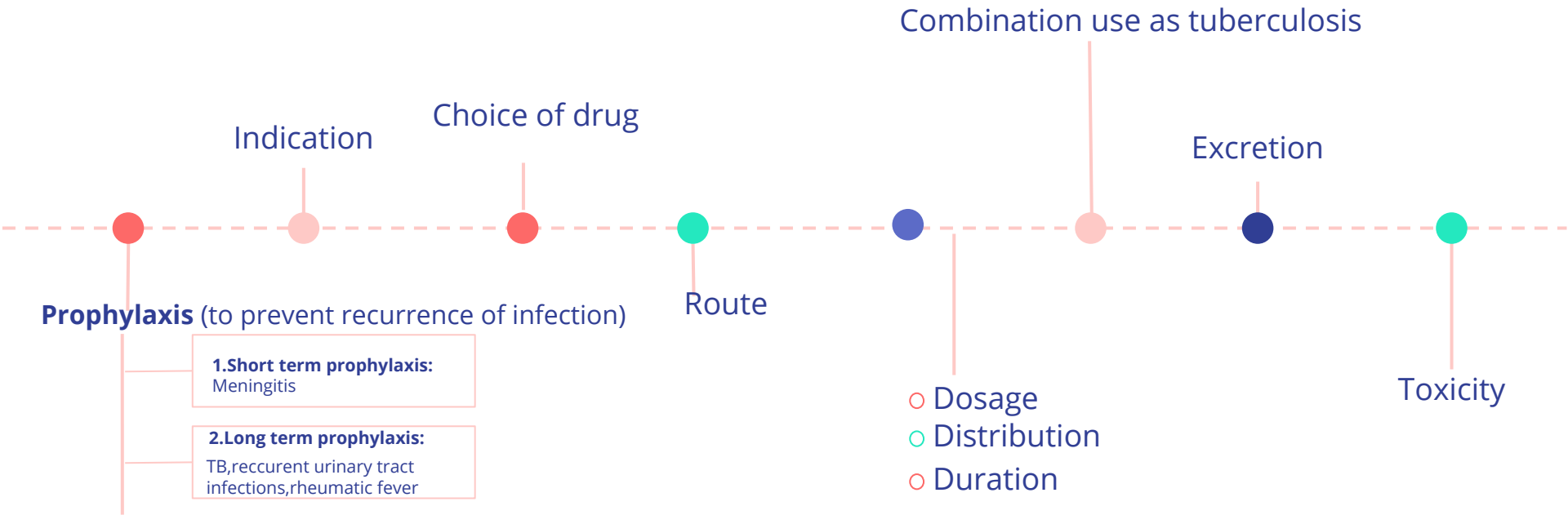
Alteration of antibiotic binding sites.

Inactivation by enzymes

Active transport out (efflux pumps) of cells



Principles of antimicrobial therapy :



Criteria for ideal antimicrobial:

- Selective toxicity
- Resistance not developed quickly
- No Hypersensitivity
- No effect on normal flora
- Penetrates tissues quickly
- Broad spectrum

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.

Quick review !

All antibiotics active on anaerobes (anti anaerobes)

1. Cell wall synthesis : carbapenem
2. Protein synthesis: Tetracyclins (30S) —> Tigycyclin & Lincosamide(50S)—> clindamycin
3. Nucleic acid synthesis: Metronidazole—> netroimidazole

All antibiotics active on gram+ve bacteria :

1. Cell wall synthesis : Benzyl penicillin & Vancomycin(glycopeptide)
2. Protein synthesis: Oxzolidonones (50S)—> linezold

All antibiotics active on gram -ve bacteria:

1. Alter cell membranes: Polymyxin B &polymyxin E (colistin)
2. Protein synthesis : Aminoglycosides

if you remember these were the examples for antibiotics with low therapeutic index

All broad spectrum antibiotics:

1. Cell wall synthesis : Carbapenem
2. Protein synthesis : Tetracyclins & chlorampenicols

All bacteriostatics :

1. Protein synthesis: Tetracyclins (30S) & Macrolides/lincosamides (50S)

Questions & Answers (MCQs)

Q1) Which of the following is considered bacteriostatic ?			
A) Tetrocyclins	B) Carbapenems	C) Macrolides	D) Both A & C
Q2) Which antibiotic has the lowest therapeutic index?			
A) Penicillin	B) Ampicillin	C) Polymyxin B	D) aminoglycosides
Q3) Streptococci and anaerobes are naturally resistant to :			
A) Aminoglycosides	B)Tigycyclin	C) Flagellin	D) polysaccharide
Q4) One of these antibiotics causes teeth discoloration:			
A) Chloramphenicol	B) Vancomycin	C) Aminoglycosides	D) Tetracycline
Q5) Which antibiotic is reserved for Tuberculosis?			
A) Rifampicin	B) Isoniazid	C) Quinolone	D) Oxazolidinone
Q6) This antibiotic SHOULD NOT be used for children < 8 years old and pregnant women:			
A) Chloramphenicol	B) Tetracycline	C) Aminoglycosides	D) Carbapenems

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

Questions & Answers (SAQ)

1. List the mechanisms of of action of antimicrobials.
2. List the antibiotics that act on anaerobes.
3. Define bacteriostatic.
4. Which antibodies act ONLY on gram +ve bacteria ?
5. What are antimicrobial agents?

Q1:
- cell wall synthesis
- protein synthesis
- nucleic acid synthesis
- alteration of cell membrane
- Anti-metabolite

Q2:
- Cefoxitin
- Carbapenems
- Tigecycline
- Clindamycin
- Nitroimidazole

Q3:
Bacteriostatics are antimicrobial agents that prevent multiplication of the bacteria.

Q4:
- Benzylpenicillin
- Vancomycin
- Oxazolidinones (Linezolid)

Q5:
- Antibiotics (natural)
- Chemotherapy (synthetic)

Team Leaders:

Reuf Alahmari Subleader: Alanoud Alhaider Abdulaziz Alqahtani

Microbiology Team
Med441

MED441
KING SAUD UNIVERSITY

Team Members:

Ghadah Alqahtani
Ghadeer Alturaifi
Leen Alrajhi
Manar Abdullah
Maram Alenazi
Nada Alsaif
Norah Alotaibi
Rana Almazrou
Reem Alkulaibi
Sarah Alhamlan
Sarah Alshammari
Shahad Almuqbil
Yara Almufleh
Abdulaziz Alqahtani
Abdullah Abdulrazaq
Ali Basfar
Bader Alshahrani
Fahad Alhifhti
Firas Alqahtani
Mohammed Alqahtani
Suliman Aldhalaan
Turki Alkhalifa
Nawaf Almadi
Ziyad Alzammam

Contact us:
microbiologyteam441@gmail.com