Microbiology team 436

436 MEDICINE KING SAUD UNIVERSITY

microbiology

LECTURE: ANTIBIOTIC

IMPORTANT.
EXTRA INFORMATION.
DOCTOR'S NOTE

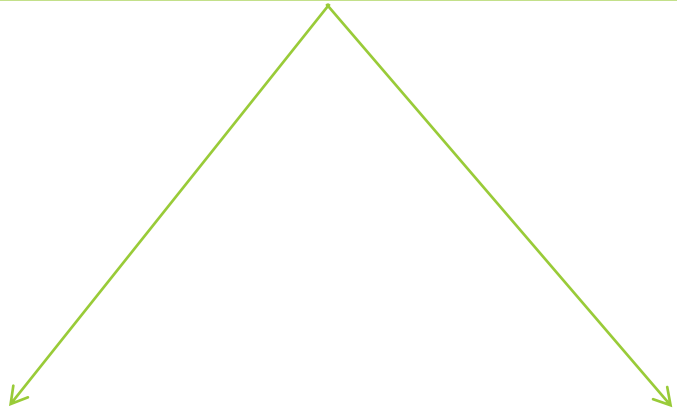
Imp → ***

جداول الصميلي موجودة آخر ثلاث سلايدز

Objectives

- *Define antibiotic, chemotherapy and selective toxicity.*
- *Describe the difference between bactericidal and bacteriostatic antibiotics*
- *Recognize the narrow and broad spectrum antibiotics*
- *Define the therapeutic index*
- *Know 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



ANTIBIOTICS:

Natural compounds produced by microorganism which inhibit the growth of other microorganism.

Like :penicillin

CHEMOTHERAPY:

- ***Synthetic compound.***
- ***Antimicrobial agents*.**

صنع الشركات مش طبيعية

❖ Toxicity

SELECTIVE TOXICITY:

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

Therapeutic Index:

The **RATIO** of the dose **toxic** to the host to the effective **therapeutic** dose.

Examples :

Penicillin → **High**

Aminoglycosides → low

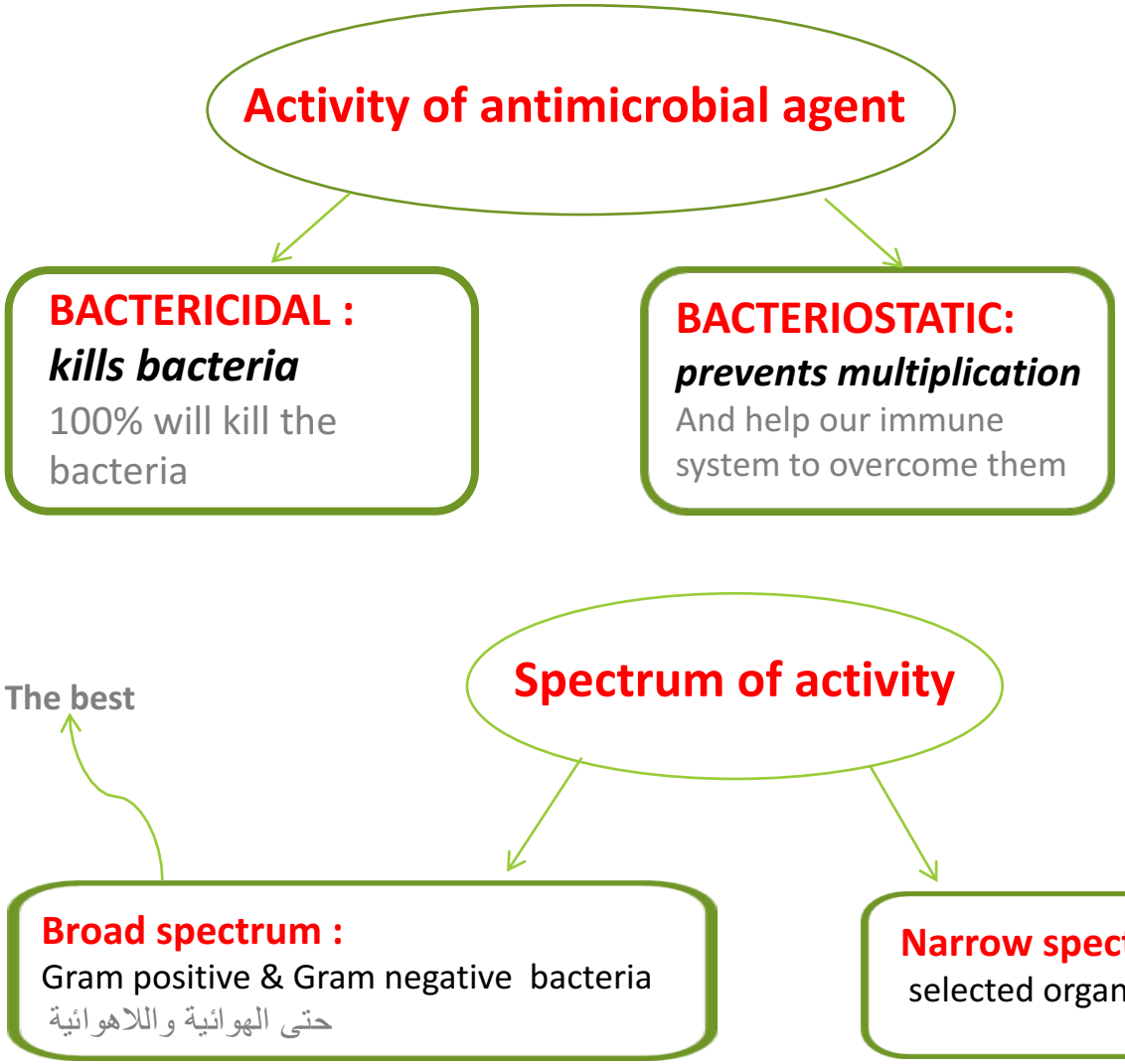
Polymyxin B → **the lowest**

High → more safety , less toxicity

$$\frac{\text{Toxic dose}}{\textit{therapeutic dose}}$$

Low → less safety , more toxicity

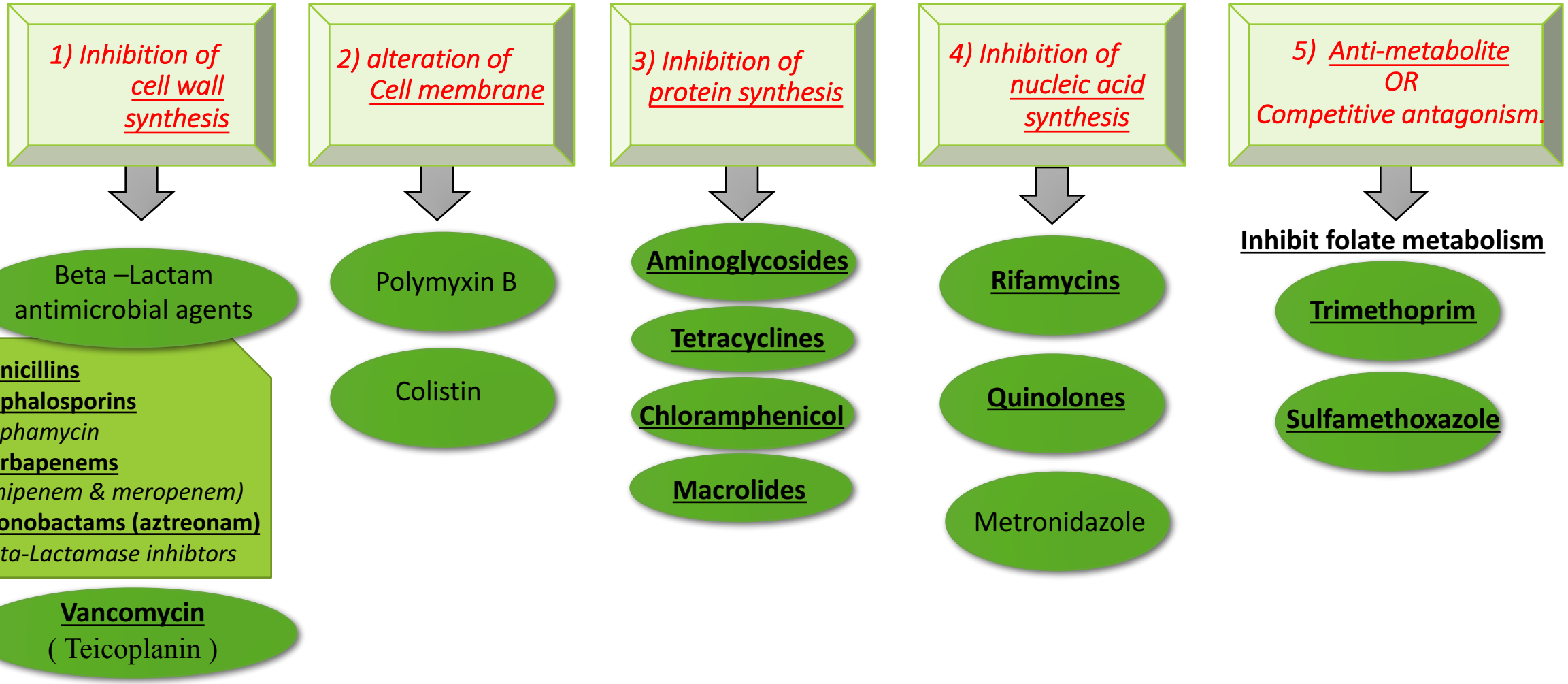
❖ Activity:



❖ Mechanisms of Action of antimicrobials

1) **Inhibition of cell wall synthesis.**
2) **alteration of cell membrane**
3) **Inhibition of protein synthesis**
4) **Inhibition of nucleic acid synthesis**
5) **Anti-metabolite OR competitive antagonism.**

❖ Mechanisms of Action of antimicrobials



❖ 1) Inhibition of cell wall synthesis

❖ Beta –Lactam antimicrobial agents

β- Lactam antibiotics

*Contain: **Beta-lactum ring** and organic acid

*It can be natural or semi-synthetic

***Bactericidal**

*Bind to penicillin binding protein (PBP) and interfere with trans-peptidation reaction.

*Toxicity: mainly
1/Hypersensitivity (allergy)
2/Anaphylaxis
3/Diarrhea

Penicillins

- Benzyl Penicillin :

Act mainly on **gram +ve**
Ex: Penicillin V
Benzathine Penicillin
Procaine Penicillin = Penicillin G

- Isoxazolyl Penicillins :

Act on **staphylococcus aureus**
Ex: **Cloxacillin**

- Amino-Penicillins :

Act on **Enterobacteria**
Ex : **Ampicillin**

- Acylaminopenicillin :

Act on **Psudomonas**
Ex: **Piperacillin**
Mezlocillin

Cephalosporins

- **1st Generation :**

Ex: Cephradine
Ceohalexine act on +ve

- **2nd Generation :**

Ex: **Cefuroxime**
Cephamycin (Cefoxitin)

- **3rd Generation** :

Expanded spectrum
Ex : **Ceftriaxone**
Ceftazidime

- 4th Generation :

Ex : Cefepim
Ceftobiprole

❖ 1) Inhibition of cell wall synthesis

❖ Beta –Lactam antimicrobial agents

Beta-Lactamase inhibitors

- β-Lactams with no antibacterial activity
- **Irreversibly bind to β-lactamase enzyme**
- Ex : Clavulanic acid, Sulbactam, Tazobactam
- Effective on staph. Penicillinases and broad spectrum β-lactamases.
- eg. amoxicillin/clavulanic acid, ticarcillin /clavulanic acid and piperacillin /tazobactam.

Beta-Lactamase area enzymes in Bacteria act on Beta –Lactam antimicrobial agents and destroy Beta-lactin ring on them , so to solve these problem we creative Beta-Lactamase inhibitors To inhibit these enzymes

❖ Vancomycin

- **Glycopeptides**
- **Bactericidal**
- *inhibit cell wall synthesis.
- Acts on **Gram positive bacteria only** (**narrow spectrum**).
- Given by **injection** only.
- Used for (**MRSA**)
  S.epidemidis
  pseudomembranous colitis
- Side effects: **Red man syndrome**
  phlebitis,
  nephrotoxic & ototoxic.

MRSA = methicillin resistant S.aureus systemic infections

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Classification of Antimicrobials

مهمMechanism of action

1) Inhibit **cell wall** synthesis

- **Beta –Lactam antimicrobial agents**
  - **Penicillins**
  - **Cephalosporins**
  - Carbapenems
  - Monobactams (aztreonam)
  - Vancomycin
- **Vancomycin** (Teicoplanin)

Note: all antibiotic cause GIT Side effect

Penicillins

Eg. Penicillin G
+ve, some anaerobes
Ampicillin
Penicillin, +ve/-ve, anaerobes
Pipracillin
Cover **Pseudomonas**

Inhibit ***peptoglycan***

Side Effect =
Hypersensitivity
=anaphylaxis shock

Cephalosphoeins

Eg. 1st generation
= Cephalexin
+ve

2nd generation
= Cefuroxime
+ve/-ve, Anaerobes

3rd generation
= Ceftriaxone
-ve

Inhibit ***peptoglycan***

Side Effect =
Hypersensitivity
=anaphylaxis shock

Glycopeptides

Eg. Vancomycin

- **Narrow** spectrum
- Cover **Only +ve**
- Used as last option

As multidrug resistance
Gram +ve

- Can be given IV

Inhibit ***peptoglycan***

Side Effect =
Red Man Syndrome
Allergy, when you give Antihistamine
= recover slowly

❖ 2) Inhibit of Cell Membrane

Polymyxin B :

- a Peptide active against **Gram negative bacteria only.**
- **Bactericidal**
- Only used locally due to serious **nephrotoxicity** when used systemically **.**

Polymyxin B Only used LOCALLY(قطرة أذن – قطرة عين) وهذا كان قديماً أما الآن فليس فقط جزئي
^وهو مضاد جديد يستخدم للحالات الصعبة جداً لفعاليته العالية , لكن مشكلته أن له نسبة سمومية كبيرة تقريباً

Colistin :

- a Peptide active against **Gram negative bacteria only.**
- used for the treatment of **multi-resistant organisms (MRO)** such as Pseudomonas and Acinetobacter infections.

2) Inhibit of Cell Membrane

Eg. Colistin & Polymyxin B

*Narrow Spectrum

*Gram –ve

*Used as multidrug resistance gram -ve

***

Side Effect

= Nephrotoxicity

❖ 3) Inhibit protein synthesis

Aminoglycosides

- **Bactericidal**
- Acts only on **Gram –ve bacteria** (**narrow** spectrum)
- **Streptococci & anaerobes are naturally resistant**
- Ex : Gentamicin
  Amikacin
  Neomycin
  Tobramycin
- Given by injection .
- Side effects :

Nephrotoxic & Ototoxic dose related.

*Aminoglycosides
S30S ribosomal subunit

Tetracyclines

- **bacteriostatic**
- **Broad spectrum**
- not used for children under 8 yrs. or pregnant women.
- Oral absorption.
- Effective for Intracellular organisms

Ex: **Mycoplasma**, **Chlamydia, Rickettsiae** ,Brucella also for V. cholera & Nocardia .

- Side effects : teeth **discoloration**
  GIT disturbance
- Classes

- Short acting: Tetracycline
- Long acting: Minocycline ,Doxycycline (good CSF penetration).
- New tetracycline : Tigycycline (covers MRSA,MSSA, some Gram negative bacteria and anaerobes)

*Tetracycline
S30S ribosomal subunit

Chloramphenicol

- **bactericidal**
- **Broad spectrum**
- Side effects :

it affects **bone marrow cells and cause aplastic anemia**

- Used only for severe infections not responding to treatment by other antimicrobials , also for the treatment of Rickettsial diseases.
- Used also topically for eye and ear infections

*Chloramphenicol
50 Sub Unit of 23 r RNA

Macrolides

- **Bacteriostatic**
- **Erythromycin & Clindamycin**
- Good activity on :Legionella, Camylobacter, **Gram negative and positive infections for patients allergic to Penicillins and Cephalosporins.**
- **Clindamycin acts on anaerobes**
- Side effects : GIT disturbance, **Pseudomembraneous colitis (mainly clindamycin).**
- New Macrolides :

Azithromycin & Clarithromycin
Less side effects , better penetration and longer half life.

*Macrolides
50 Sub Unit of 23 r RNA

** you don't have to know them actually, just for your knowledge the ribosome is compose of two subunit the large is 50S and the smal is 30S

3) Inhibit **protein synthesis**

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Aminoglycosides

- Eg. Gentamicin
  Amikacin
  Tobramycin
  neomycin
- All are gram –ve
  Bactericidal
  Narrow spectrum
- Side Effect
  = **Otoxicit and Nephrotoxicity**

8th nerve effect ear and balance
Increase drug = effect bone nerve
No renal problems

Tetracyclines

- **Broad** Spectrum
- Spectrum of activity
  = Rickettsiae
  Mycoplasma
  Clamydia
- Side Effect
  = **Discoloration in children**
  Pregnant = destruct bone of baby

Chloramphenicol

- Spectrum of activity
  the treatment of Rickettsial diseases
- Side Effect
  = bone marrow
  a plastic anemia

Bone Marrow Suppression

Macrolides & Lincosamides

- Eg. Erythromycin & Clindamycin
  = **Broad** spectrum
- Eg. Clindamycin
  = spectrum **acts on anaerobes**
- New Macrolides :
  Azithromycin
  Clarithromycin
- Side Effect
  = **GIT pseudo-membranous Colitis**

❖ 4) Inhibition of nucleic acid synthesis.

Rifampicin

- **Bactericidal**
- Semi-synthetic
- acts on **Gram positive bacteria and selected Gram negative bacteria**.
- **Reserved for Tuberculosis (Anti TB)**
- Resistance develops quickly
- Used in combination
- Side effects : hepatotoxicity. & discoloration of body fluids

Metronidazole

- **Bactericidal**
- **Nitroimidazole active on anaerobic bacteria and also parasite.**
- Causes DNA breakage.
- Used for the treatment of infections due to **B.fragilis** , Trichomonas vaginalis and also for amoebiasis and giardiasis. (Antiprotozoal)

Quinolones

- **Bactericidal**
- Synthetic, bactericidal
- inhibit DNA Gyrase and /or Topoisomerase.
- Generations:
  - 1st Generation: Nalidexic acid locally acting (Broad spectrum)
  - 2nd Generation: **Fluoroquinolones** (Narrow : Gram –ve)

Ex. **Ciprofloxacin**, Norfloxacin, Ofloxacin,Levofloxacin

  - 3rd Generation: Sparfloxacin, Gatifloxacin
  - 4th Generation: **Moxifloxacin**, Trovafloxacin (Anaerobes)
- Side effects: affects cartilage & heart

4) Inhibition of **nucleic acid** synthesis.

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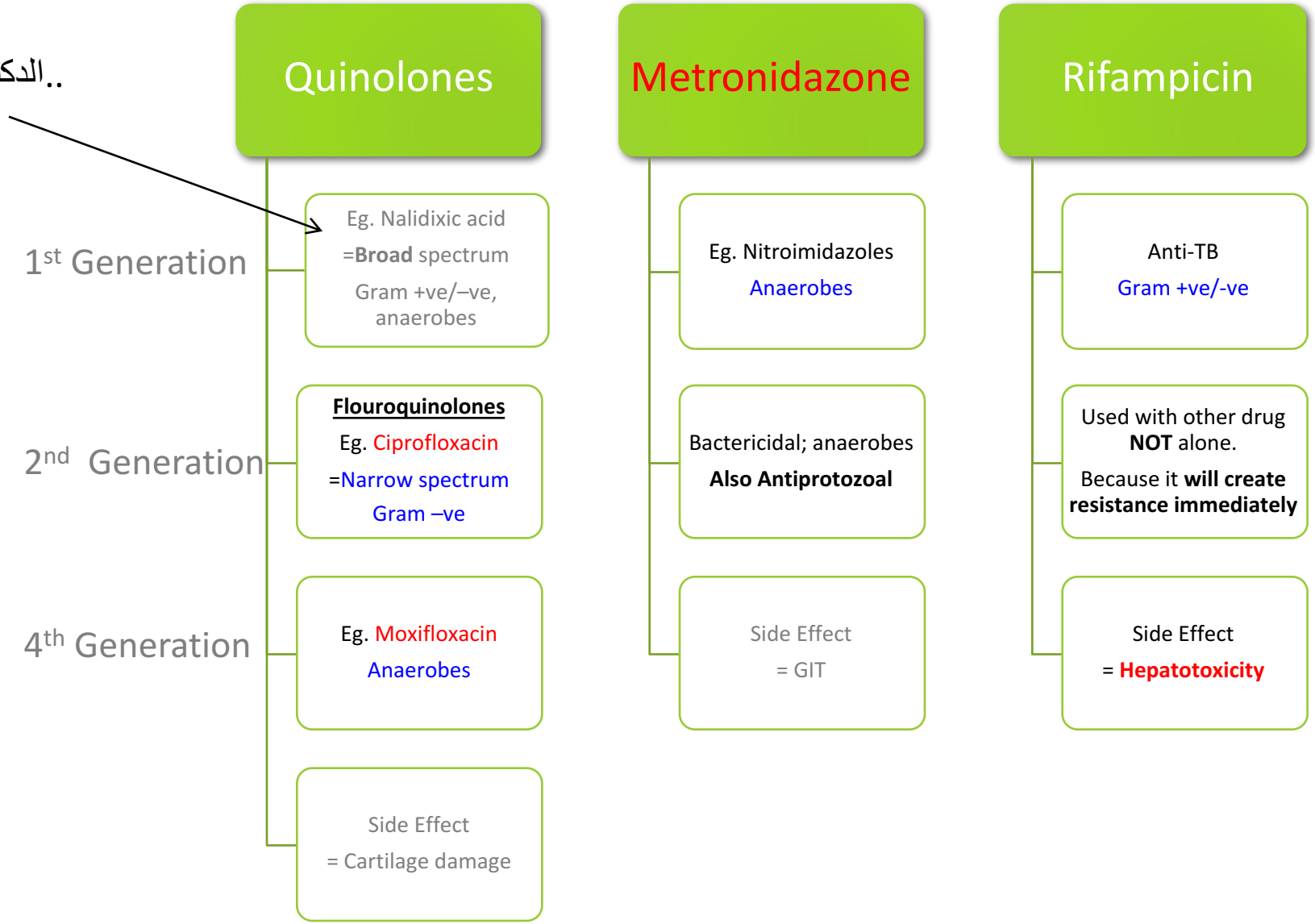
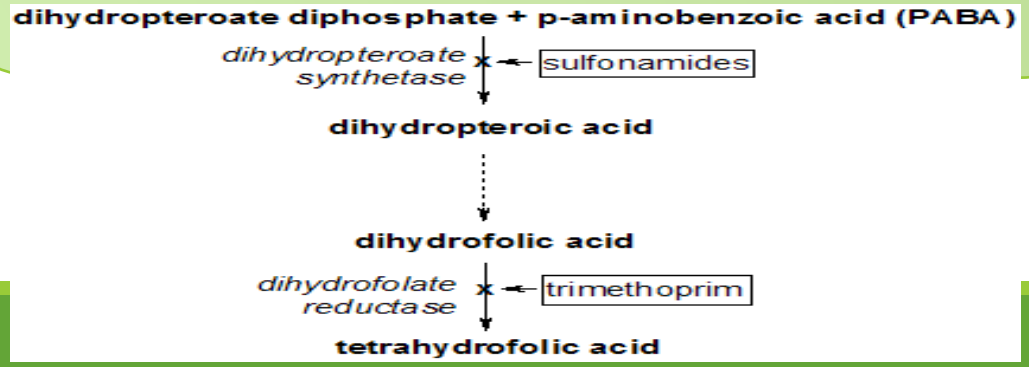
الدكتور تكلم عنها بس ما ضللها بالجدول..



❖ 5) Antimetabolites (Folate inhibition)

- **Bacteriostatic**
- **Trimethoprim-Sulfamethoxazole (TMP-SMX)**
- *Combination of TMP-SMX called* : Bactrim / Septrin (اسم تجاري)
- Block sequential steps in **folic acid synthesis**
- *Used to treat :* ***Nocardia, Chlamydia, Protozoa & P.cranii infection.***
- Used for the treatment of: upper & lower respiratory tract infections , otitis media, sinusitis & infectious diarrhea.
- Side effects: GIT, hepatitis , bone marrow depression, hypersensitivity



5) Inhibit **folate** metabolism/ bacterial growth

Trimethoprim
Sulfamethoxazole

Sulfonamides

- Eg. Sulfadiazine
- **Blocks folic acid synthesis**
- **Bacteriostatic**
  Grame –ve
  Used a lot in hospital
- Side Effect
  = GIT

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❖ Classification of Antimicrobials

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1) Inhibition of cell wall synthesis

- Beta –Lactam antimicrobial agents
  - **Penicillins**
  - **Cephalosporins**
  - **Carbapenems** *(imipenem & meropenem)*
  - **Monobactams (aztreonam)**
- **Vancomycin**

3) Inhibition of protein synthesis

- **Aminoglycosides**
- **Tetracyclines**
- **Chloramphenicol**
- **Macrolides**
- **Clindamycin**
- **Oxazolidinones (linezolid)**
- **Streptogramins**
- **Quinupristin dalfopristin**

4) Inhibition of nucleic acid synthesis

- **Rifamycins**
- **Quinolones**
- Metronidazole

5) Anti-metabolite OR Competitive antagonism.

Inhibit folate metabolism

- **Trimethoprim**
- **Sulfamethoxazole**

Miscellaneous

- **Metronidazole**
- **Daptomycin**

Miscellaneous : including many thing of different kinds

###مهم تعرف الامثلة تحت كل نوع ممكن يسألك بالإختبار(تحتها خط)

Bactericidal and Bacteriostatic تحت ال مهم تعرف الامثلة###

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Bactericidal

- Penicillin
- Cephalosporins
- Carbapenems
- Monobactams
- Vancomycin
- Aminoglycosides
- Fluoroquinolones
- Metronidazole
- Rifampin
- Isoniazid

Bacteriostatic

- Tetracyclines
- Doxycycline
- Macrolides
- Sulfonamides

Can cause Nephrotoxicity as side effect

- ✓ Aminoglycosides
- ✓ Colistin & Polymyxin B

Can cause hepatotoxicity as side effect

- ✓ Rifampin

Can cause Hypersensitivity as side effect

- ✓ Penicillins
- ✓ Cephalosphorins

We can not use it with pregency women

- ✓ Tetracyclines

Narrow spectrum

Antibiotic for Anaerobic

- ✓ Metronidazole
- ✓ Moxifloxacin
- ✓ Clindamycin

Antibiotic for +ve gram only

- ✓ Vancomycin
- ✓ Cephalexin

Antibiotic for -ve gram only

- ✓ Colistin & Polymyxin B
- ✓ Aminoglycosides
- ✓ Fluoroquinolones
- ✓ Sulfadiazine

❖ Antituberculous agents:

First line:

- Isonlazide (inh)
- Rifampicin
- Ethambutol
- Pyrazinamide

second line:

- streptomycin
- PASA
- cycloserine,
- capreomycin

If the 1st line does not work, they use the 2nd line

###مطالبين فقط بال Side Effect

Anti TB isoniazide (INH)

Side Effect
= Hepatotoxicity peripheral neuropathy
+ turn urine and tears into red/pink

Elhambiotd

Side Effect
= Optic neurititis
(color blindness)
+ Hepatotoxicity

Pyrazinamide

Side Effect
= Hepatitis, arthraglia (gout)

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Antibiotics class	ACTION	USE	S/E
Anti TB isoniazide (INH)	Bacteriocidal All lung tissue	T.B treatment and prophylaxis	Hepatotoxicity peripheral neuropathy (pyridoxine (vitamin B6))
Elhambiotd	bactericidal concentrated lung alveoli phagolysosome	TB treatment	Optic neurititis
Pyrazinamide	Acid environment of macrophages	TB treatment	Hepatitis, arthraglia (gout)

Antibiotic Resistance in Bacteria

Types of Resistance			
Innate resistance (primary resistance)	Acquired resistance (primary resistance)		Selective pressure resistance
○ Naturally resistance. Called **Constitutive** resistance. ○ Eg: *Streptococcus* & anaerobes are resistant to gentamicin.	1) Mutation: Ex: Mycobacterium Resistance to Streptomycin . ○ Called **Vertical** ○ Mutation during replication in DNA formation ○ Mother to child	2) Gene Transfer: Acquired from other bacteria Called **Horizontal** Either **Plasmid** mediated using **sex pilli** (resistance transferred within same species) Or through **Transposons** (can transfer resistance from gram +ve to –ve)	Bacteria Mutant (like 1 in 10000) And when Antibiotic used lead to kill all sensitive stray Resulting in survival of resistance stray

Cross resistance :

- Resistance to one group confer resistance to other drug of the same group .

eg. Resistance to **erythromycin** and **clindamycin**

Dissociate resistance:

- resistance to **gentamicin** does not confer resistance to **tobramycin** .

Antibiotic Resistance in Bacteria

Mechanisms of resistance	Principles of antimicrobial therapy	Criteria for ideal antimicrobial agent
1- **Permeability** changed 2- **Modification** of site of action, e.g. Mutation. 3- **Inactivation** by enzymes . E.g. Beta- Lactamase & aminoglycoside inactivating enzymes. 4- Passing **blocked metabolic reaction** e.g. PABA (para amino benzoic acid) à ☾ folic acid , and is plasmid mediated.	❖ Indication ❖ Choice of drug ❖ Route ❖ Dosage ❖ Duration ❖ Distribution ❖ Excretion ❖ Toxicity ❖ Combination use as in tuberculosis (SYNERGISTIC, ANTAGONISTIC or ADDIDITIVE) ❖ USE (PROPHYLAXIS, EMPIRIC or DEFINITE) Short term: Meningitis Long term: Tuberculosis, rheumatic fever recurrent urinary tract infections,	❖ Has **selective** toxicity ❖ Causes **no hypersensitivity** ❖ **Penetrate** tissues quickly ❖ Resistance **does not** develop quickly ❖ Has **no effect** of normal flora ❖ **Broad** spectrum **## مهمة ^^**

Antibiotics class	Examples	Mechanisms	Spectrum of Activity	S/E
INHIBITION OF CELL WALL				
Penicillins	Natural; penicillin G Semi-synthetic: oxacillin, ampicillin-clavulanic acid, ampicillin-sulbactam Pipracillin	Inhibit peptoglycan synthesis necessary for cell-wall formation	Bactericidal-most active against gram +; synthetic and potentiated penicillin have improved gram – coverage Penicillin G +ve, some anaerobes Ampicillin Penicillin, +ve/-ve, anaerobes Pipracillin Cover **Pseudomonas**	Hypersensitive, anaphylaxis GIT
CEPHALOSPHORINS	1ST generation: cephalothin, cephalexin, 2nd generation: Cefuroxime 3rd generation: ceftriaxone, ceftazidime 4th generation: cefepime		Bactericidal 1st gen: Gram +, limited Gram - 2nd gen: Gram+, improved Gram – and some anaerobes. 3rd gen: limited Gram+, excellent Gram- and anaerobes	
Glycopeptides	Vancomycin	Inhibit Peptidoglycan synthesis	Bacteriocidal; Gram+ve bacteria only MRSA	Red man syndrome Nepro and ototoxicity
Inhibition of cell Membrane				
Polymyxin	Colistin	Alter cell memnrano permeability	Bacteriocidal; Gram-ve bacteria	Nephrotoxicity

Antibiotics class	Examples	Mechanisms	Spectrum of Activity	S/E
Inhibition of protein synthesis (Ribosome)				
Aminoglycosides	Gentamicin, amikacin, tobramycin, neomycin	Bind 30S ribosomal subunit; inhibit peptide elongation	Bactericidal; Gram-, includingPseudomonas and Mycobacterium, Streptococcus and anaerobes are resistant	Ototoxicity snd Nephrotoxicity
Tetracyclines	Tetracyclines, doxycycline	Bind 30S subunit; inhibit RNA function	Bacteriostatic; Gram+ and Gram -; Rickettsiae, Mycoplasma, Clamydophila	Teeth discoloration GIT photosensitivity
Chloramphenicol	Chloramphenicol	Bind 50S subunit, inhibit protein synthesis	Bacteriostatic; broad Gram+ and Gram- spectrum	BM a plastic anemia
Macrolides and lincosamides	Erythromycin Azithromycin Clarithromycin Clindamycin	Bind 50S subunit; inhibit protein synthesis	Bacteriostatic; Gram+, Legionella, Camphylobacter, Mycoplasma, Chlamydophila, Ricketstsiae, good anaerobic spectrum	GIT pseudo-membranous colitis

Antibiotics class	Examples	Mechanism	Spectrum of Activity	S/E
INHIBITION OF NUCLEIC ACID SYNTHESIS				
Flouroquinolones	Nalidixic acid, Ciprofloxacin, Gatifloxacin Moxifloxacin	Inhibits DNA gyrase, preventing supercoiling →DNA degradation	Bactericidal; Gram +ve and gram -ve, INCLUDING Pseudomonas at a higher dosage	Cartilage damage
Nitroimidazoles	Metronidazole	Metabolized by anaerobes to intermediates that prevent DNA synthesis	Bactericidal; anaerobes (Also antiprotozoal)	GIT
Rifampicin	Rifampicin	DNA degradation	Bactericidal; Gram +ve and gram –ve bacteria	Discoloration of body fluid hepatotoxicity
INHIBITION OF BACTERIAL GROWTH				
Sulfonamides	Trimethoprim-sulfadiazine, ormethoprim sulfa	Competitive analogue of para-aminobenzoic acid (PABA) →inhibits dihydrofolate reductase →blocks folic acid synthesis	Bacteriostatic → bactericidal when combined. Gram –ve Chlamydia, nocardia, protozoa and pneumocystic	GIT

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