ANTIBIOTICS

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Lecture Objectives..

- **By the end of this lecture the student should be able to:**
  - 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

Lecture Objectives..

- Recall the mechanism of action of antimicrobial agents.
- Recognize the various classes of antimicrobial agents and important agents within the classes (action, spectrum and side effects)
- Explain the criteria for an ideal antimicrobial

Definitions/Terminologies

ANTIBIOTICS:

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

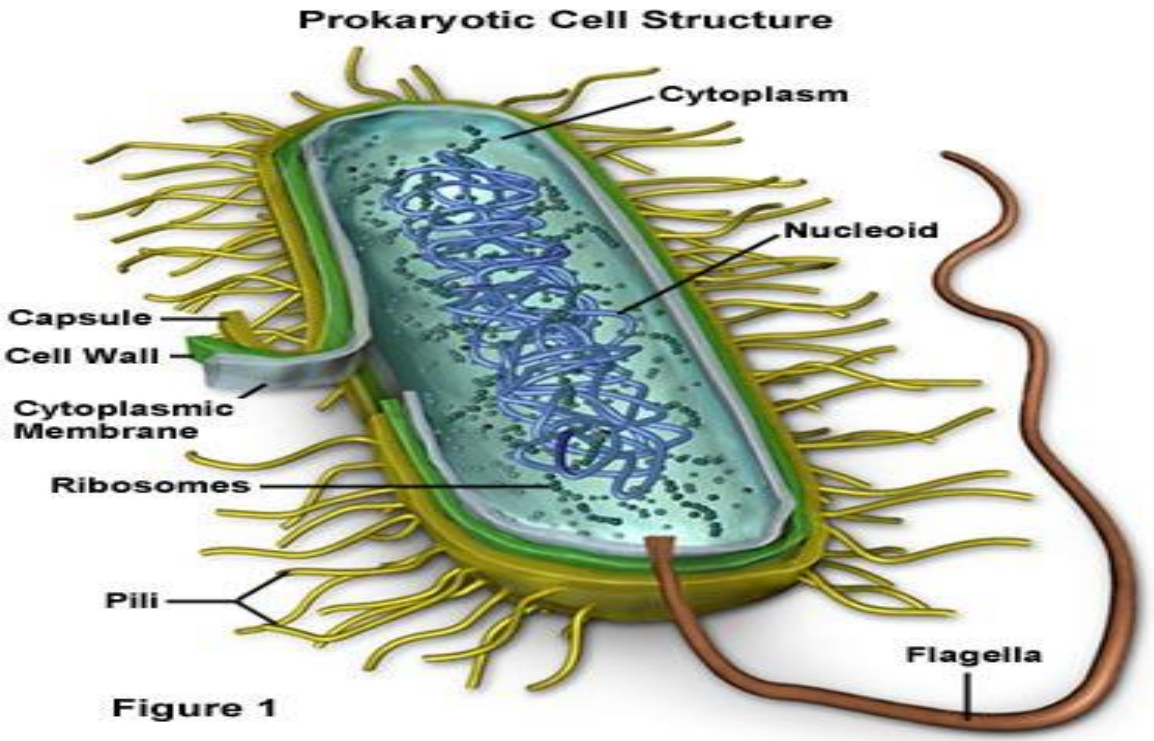
CHEMOTHERAPY:

Synthetic compounds .

All together are called Antimicrobial Agents.

SELECTIVE TOXICITY

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



BACTERICIDAL **: Antimicrobial agent that kills the bacteria**

BACTERIOSTATIC : **: Antimicrobial agent that prevents multiplication of the bacteria.**

Spectrum of activity

Broad spectrum : **Antimicrobial agent that affects Gram positive & Gram negative bacteria**

Narrow spectrum : **Antimicrobial agent that affects only selected organisms or group of bacteria (G+VE,or G-VE).**

THERAPEUTIC INDEX

The Ratio of Toxic dose to human / Therapeutic dose against bacteria.

Examples:

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

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

1) **Inhibition of cell wall synthesis.**

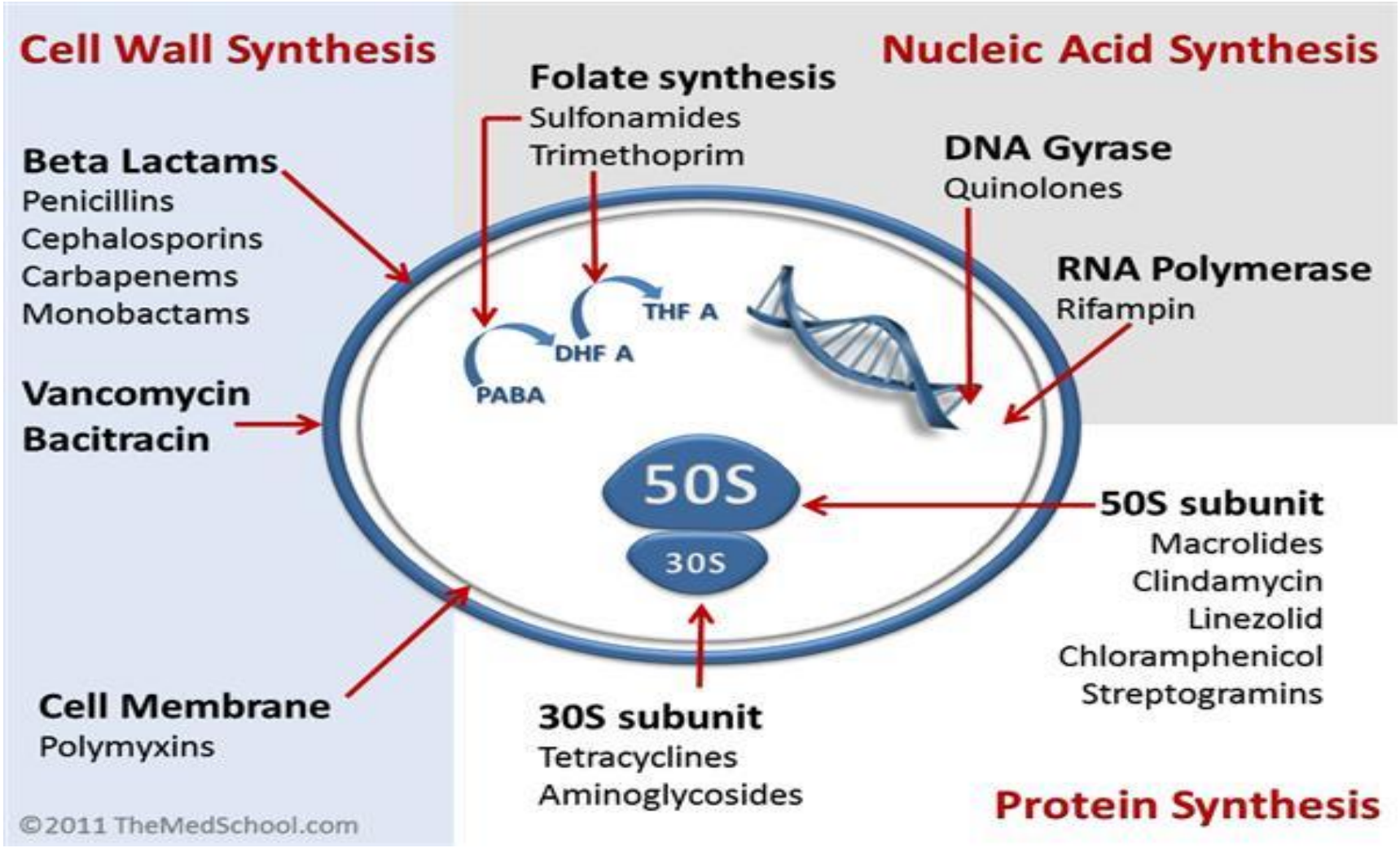
2) **Alteration of cell membrane.**

3) **Inhibition of protein synthesis.**

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

5) **Anti-metabolite *OR* competitive antagonism.**

Mechanisms of action of antimicrobial agents



ANTIMICROBIALS THAT INHIBIT CELL WALL SYNTHESIS

- **1- Beta – Lactam antimicrobial agents are :**

  Penicillins

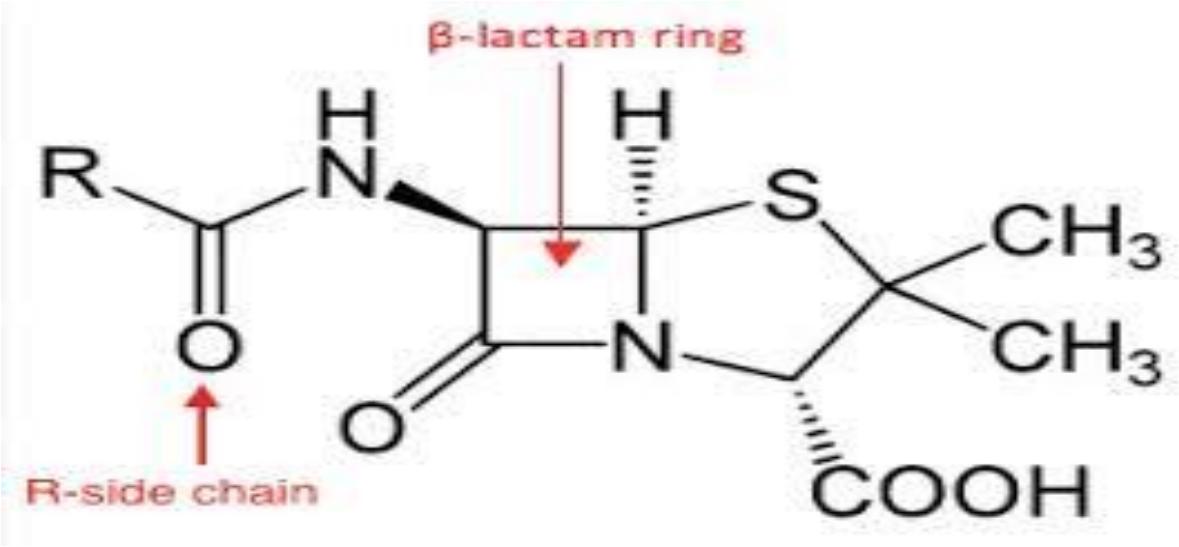
  Cephalosporins

  Carbapenems

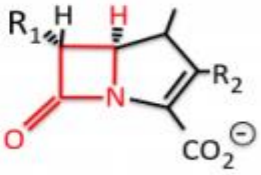
  Monobactam

  Beta lactamase inhibitors

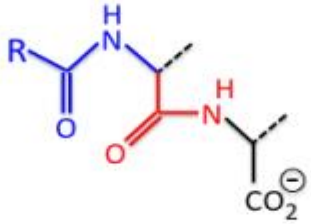
- **2- Glycopeptides :** eg. Vancomycin



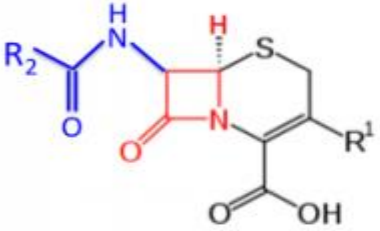
penicillins



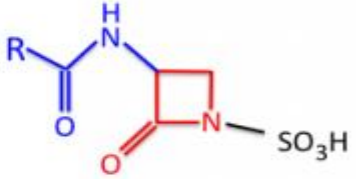
carbapenems



acyl-D-Ala-D-Ala
(cell wall precursor)

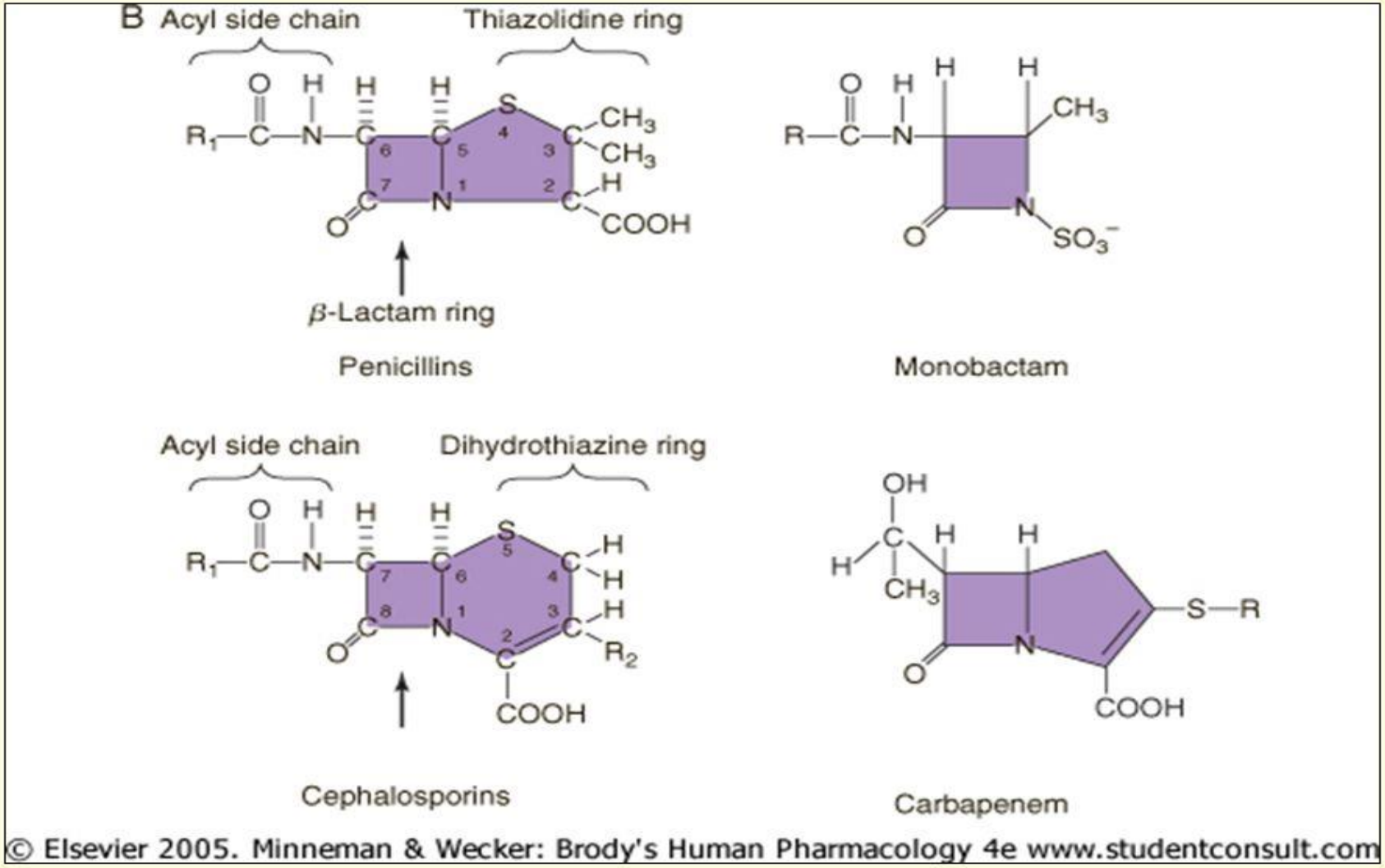


cephalosporins



monobactams

Beta-Lactam Antibiotics

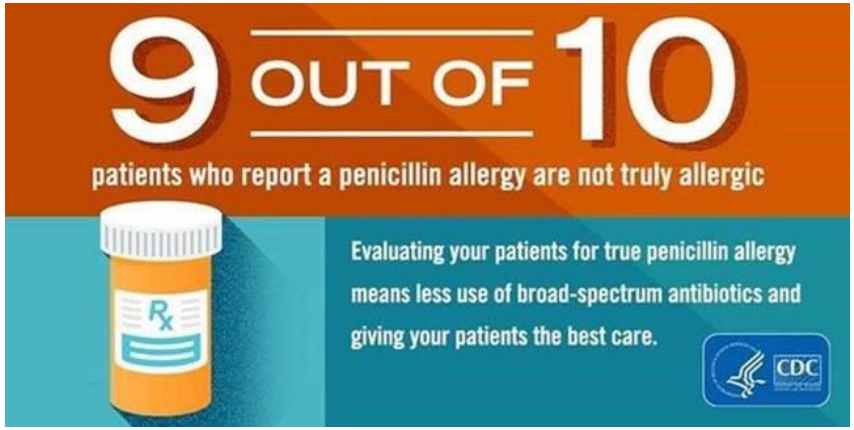


β - LACTAM ANTIBIOTICS

- Composed of : **Beta- Lactam ring** & **Organic acid**.
- Natural & Semi-synthetic
- Bactericidal
- Bind to Penicillin Binding Protein (*PBP*)and interfere with trans-peptidation reaction that lead to cell wall destruction.

Toxicity: common include :

- Allergy (common)
- Anaphylaxis (serious)
- Diarrhea.



Penicillins

Benzyl penicillin :acts mainly on Gram positive bacteria, examples;

- **Penicillin V ,Procaine penicillin & Benzathine penicillin**

***Isoxazolyl penicillins*: Cloxacillin** –effective for *Staphylococcus aureus.*

***Amino-penicillins*: Ampicillin** – effective for *Enterobacteria*.

***Acylaminopenicillins*: Piperacillin**- effective for *Pseudomonas.*

CEPHALOSPORINS

First Generation:

.Effective on Gram positive & some Gram negative bacteria

- Cefazolin, cephalexin

Second generation:

.Effective on Gram positive & some Gram negative bacteria: cefuroxime

.Acts on Anaerobes: cefoxitin

Third generation:

.Expanded spectrum

. Effective on Gram negative & some Gram positive bacteria: ceftriaxone

.Effective on *Pseudomonas: ceftazidime*

Fourth generation:

.Effective on Gram negative and some Gram positive bacteria:

Cefepime

Fifth generation:

.Effective on multi resistant Gram positive & Gram negative bacteria:

Ceftobiprole

β-Lactamase inhibitors

- β-Lactams with limited antibacterial activity
- Irreversibly bind to β-lactamase enzyme
- Clavulanic acid, Sulbactam, Tazobactam
- Effective on Staph. Penicillinases and broad spectrum β-lactamases.
- eg. amoxicillin/clavulanic acid, ticarcillin /clavulanic acid and piperacillin /tazobactam.

Carbapenems

- Beta-lactams.
- Cover gram positive ,gram negative bacteria as well as anaerobes (**broad spectrum**).
- **Restricted to critically ill patients or patients infected with multi-resistant organisms .**
- Given by injection.
- eg. Imipenem & Meropenem.

VANCOMYCIN

- A Glycopeptide, inhibits cell wall synthesis.
- Bactericidal . Acts on **Gram positive bacteria only** (*narrow spectrum*).
- Given by **injection**
- Used for systemic infection by methicillin resistant *Staphylococcus aureus* (**MRSA**), empirical treatment of Gram positive infections & pseudomembranous colitis.

- **Side effects:**

nephrotoxicity & ototoxicity, phlebitis, Red man syndrome

ANTIBIOTICS THAT ALTER CELL MEMBRANES

Polymyxin B and Colistin (polymyxin E):

- **a Peptide, active against Gram negative bacteria only (narrow spectrum).**
- **Bactericidal.**
- **Used to treat multi-resistant infection caused by Gram negative bacteria such as Pseudomonas and Acinetobacter infections.**
- **Risk of nephrotoxicity.**

ANTIBIOTICS THAT INHIBIT PROTIEN SYNTHESIS

- **AMINOGLYCOSIDES, binds 30s ribosomal subunit**
- **TETRACYCLINES, binds 30s ribosomal subunit**
- **CHLORAMPHENICOL, binds 50s ribosomal subunit**
- **MACROLIDES/LINCOSAMIDE, binds 50s ribosomal subunit**
- **OXAZOLIDONONES, binds 50s ribosomal subunit**

AMINOGLYCOSIDES

1. Bactericidal
2. Acts only on Gram negative bacteria (*narrow spectrum*)
3. Streptococci & anaerobes are naturally resistant.
4. Examples: Gentamicin, Amikacin , Neomycin .
5. Given mainly by injection
6. **Side effects :** dose related Nephrotoxicity & Ototoxicity.

TETRACYCLINS

- Broad spectrum , bacteriostatic. Given by oral route.
- Effective for Intracellular organisms eg. *Mycoplasma, Chlamydia ,Brucella* also effective for *Nocardia* and *Vibrio cholerae*.

Classes

- Short acting: Tetracyclin
- Long acting: Minocycline , Doxycycline (good CSF penetration).
- **New tetracycline** : Tigycyclin *(covers multiresistant Gram positive and some Gram negative bacteria and anaerobes).*
- **Side effects :** Permanent teeth discoloration , GIT disturbance
- **Should NOT be used for children < 8 year old and pregnant women.**

CHLORAMPHENICOL

- Broad spectrum & bactericidal
- Serious side effects : it affects bone marrow cells and cause a plastic anemia.
- Limited use nowadays : only for severe infections not responding to treatment by other antimicrobials .
- can be applied *topically (locally)* for eye and ear infections.

MACROLIDES / LINCOSAMIDES

- Erythromycin (*Macrolide*)
- Clindamycin (*Lincosamide*)

- **Both are Bacteriostatic**
- **Macrolides active on: *Legionella, Camylobacter*, Gram negative and positive infections *for patients allergic to Penicillins and Cephalosporins* including oral infections.**
- **Clindamycin acts on Staphylococci, Streptococci and anaerobes**
- **Side effects : GIT disturbance, Pseudomembraneous colitis (mainly *clindamycin*).**
- **New Macrolides :**

Azithromycin & Clarithromycin .

Less side effects , better tissue penetration and longer half life.

Oxazolidonones

Linezolid

- Inhibits protein synthesis
- Used to treat multi-resistant gram positive bacterial infections.
- **Common side effects:**
  - Thrombocytopenia
  - Diarrhea

ANTIMICROBIALS THAT ACT ON NUCLEIC ACID

- **Rifampicin**
- **Quinolones**
- **Metronidazole**

RIFAMPICIN

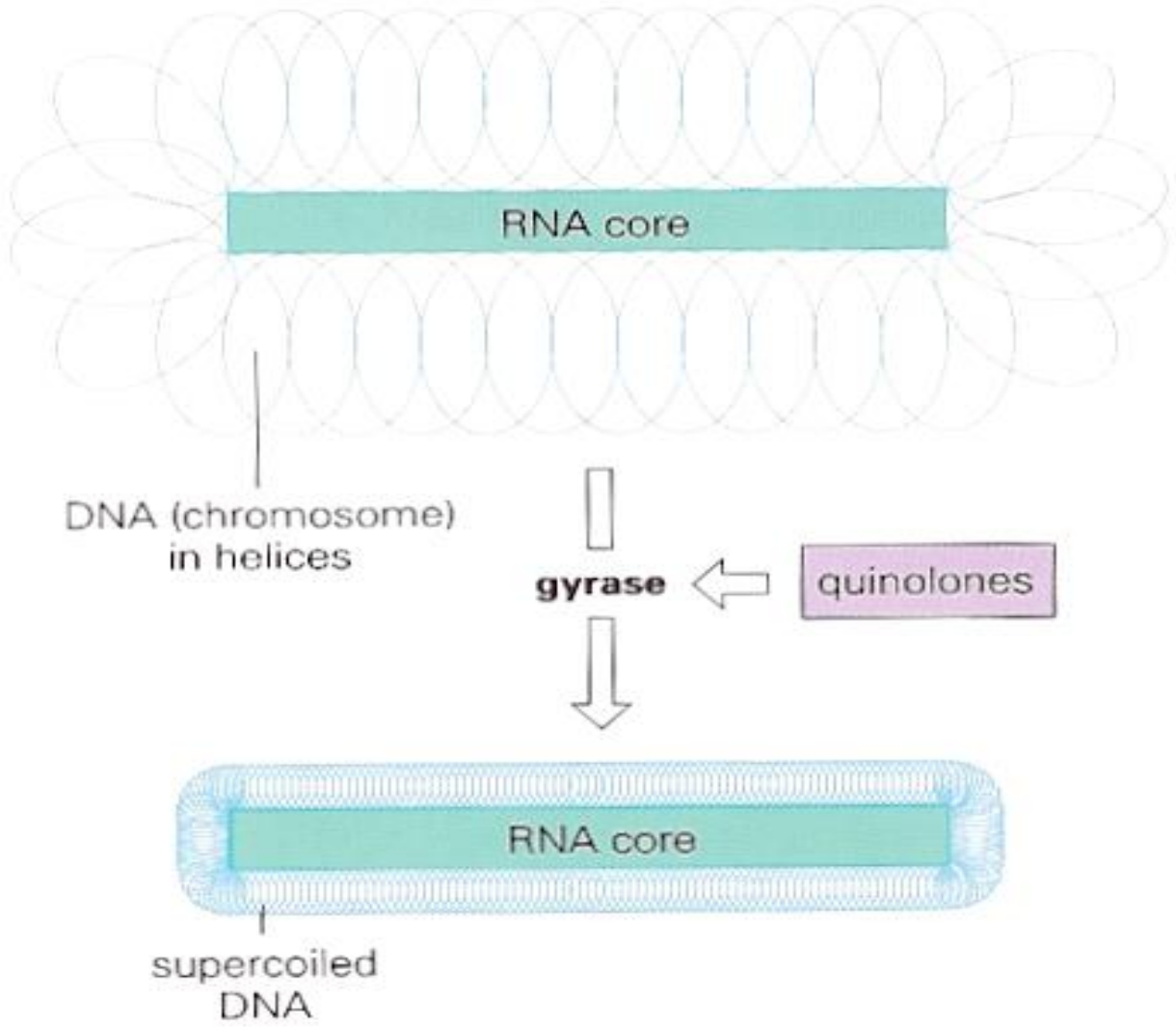
- **Semi-synthetic, bactericidal , acts on Gram positive bacteria and selected Gram negative bacteria.**
- **Reserved for Tuberculosis**
- **Resistance develops quickly. Must be used in combination with other antimicrobial agent.**
- **Side effects: Causes discoloration of body fluids & hepatotoxicity.**

QUINOLONES

- Synthetic, bactericidal, inhibit DNA *Gyrase* and /or Topoisomerase.
- **Generations:**
- ***first generation***: Nalidexic 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
  Should be used with caution for patients under 18 year and pregnancy.

TARGET SITE FOR QUINOLONES

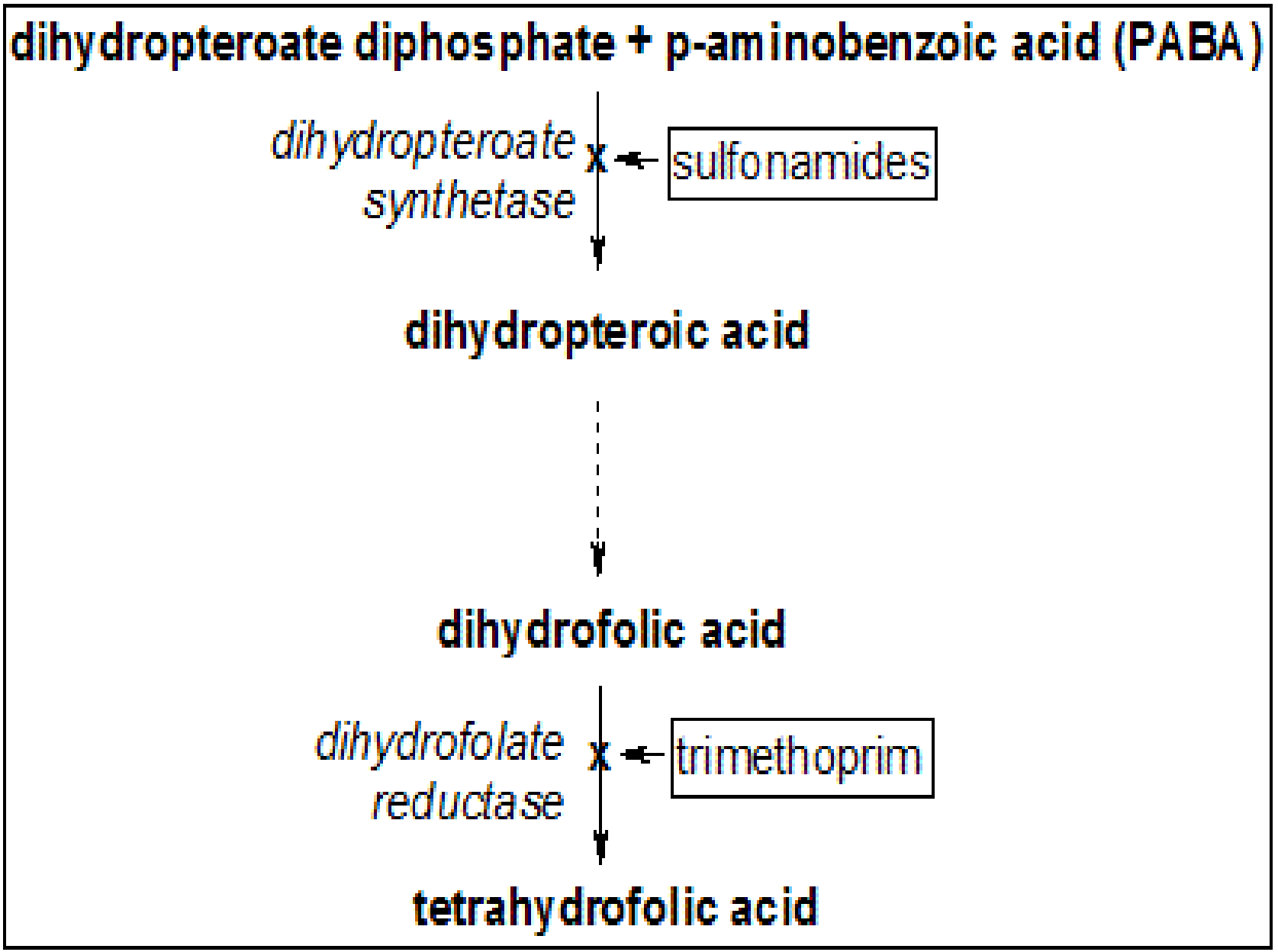


Metronidazole

- **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)

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


dihydropteroate diphosphate + p-aminobenzoic acid (PABA)
dihydropteroate synthetase
sulfonamides
dihydropteroic acid
dihydrofolic acid
dihydrofolate reductase
trimethoprim
tetrahydrofolic acid

Anti-tuberculosis agents

First line agents

- Isoniazid (INH)
- Rifampicin
- Ethambutol
- Pyrazinamide

A combination of 3 or 4 drugs used for 4-6 months.

eg. INH+ Rifampicin + Ethambutol + Pyrazinamide for 2 months then continue INH + Rfampicin for 4 months.

Second line agents

- Sterptomycin
- Para amino salicylic acid (PASA)
- Cycloserine
- Capreomycin

Used for resistant cases or cases not responding to first line drugs.

ISONIAZIDE (INH)

- Bactericidal
- Inhibits mycolic acid synthesis
- Affects mycobacteria at different sites of lung tissues
- Used for the treatment & prophylaxis of tuberculosis
- Can cause peripheral neuritis (pyridoxine (vitamin B6) added in certain patients) and hepatitis

Ethambutol

- Affects cell wall synthesis
- Optic neuritis

Pyrazinamide

- Exact mechanism unknown
- Hepatitis & arthralgia

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:

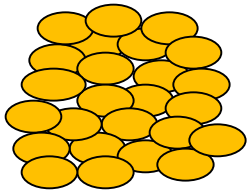
Primary (Innate) resistance eg. *Streptococcus* & anaerobes are naturally resistant to Gentamicin.

Secondary (acquired) resistance due to**:**

- Mutation

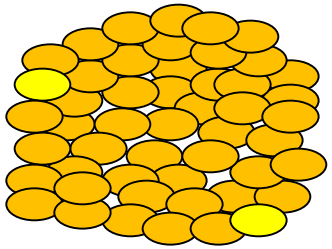
-Gene transfer (e.g. plasmid mediated or through transposons)

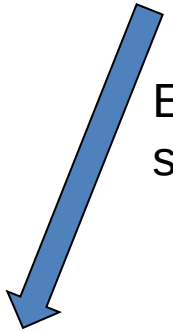
Antimicrobial Selection of Resistance



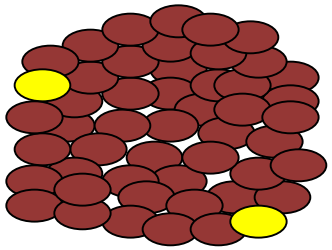
Bacterial Population

Spontaneous mutations
during replication and division

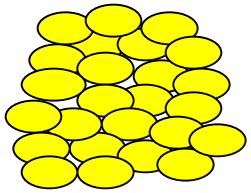


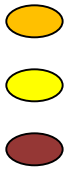


Exposure to
selecting antibiotic



Susceptible population killed,
mutants survive & proliferate



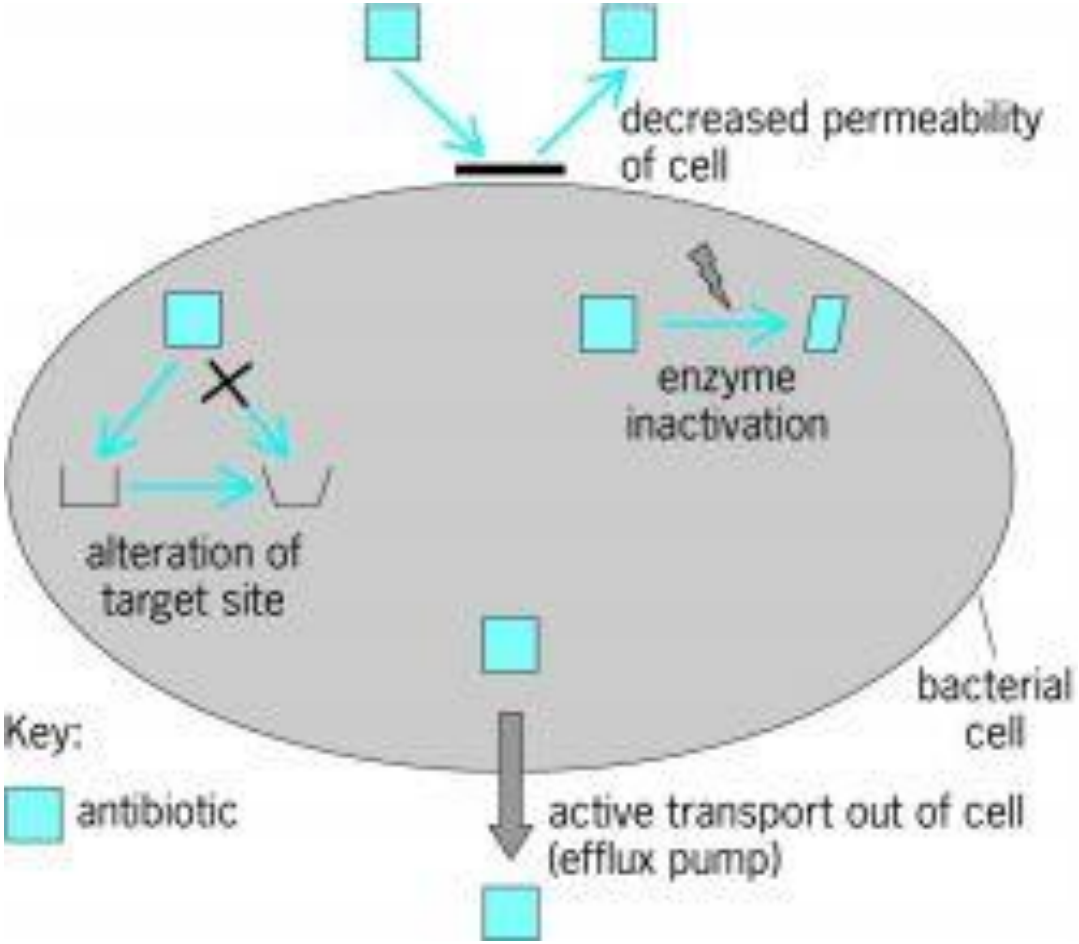


Wild type
Resistant
Dead

Mechanisms of Resistance to Antimicrobial Agents

1- Decreased permeability to antimicrobial agent.
2- Alteration of antibiotic binding sites.
3- Inactivation by enzymes .
4- Active transport out (efflux pumps) of cells

Mechanisms of Resistance to Antimicrobial Agents



PRINCIPLES OF ANTIMICROBIAL THERAPY

- **INDICATION**
- **CHOICE OF DRUG**
- **ROUTE**
- **DOSAGE**
- **DURATION**
- **DISTRIBUTION**
- **EXCRETION**
- **TOXICITY**

- **COMBINATION USE AS IN TUBERCULOSIS**
- **PROPHYLAXIS.**

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
- PENETERATE TISSUES QUICKLY
- RESISTANCE NOT DEVELOP QUICKLY
- NO EFFECT ON NORMAL FLORA
- BROAD SPECTRUM

Reference book and the relevant page numbers..

- **Sherries Medical Microbiology, an introduction to Infectious Diseases.** Latest edition, Kenneth Ryan and George Ray. Publisher: Mc Graw Hill.

Take home messages

- **Antibiotics can do harm, resistance can develope 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.**