



# **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(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 .

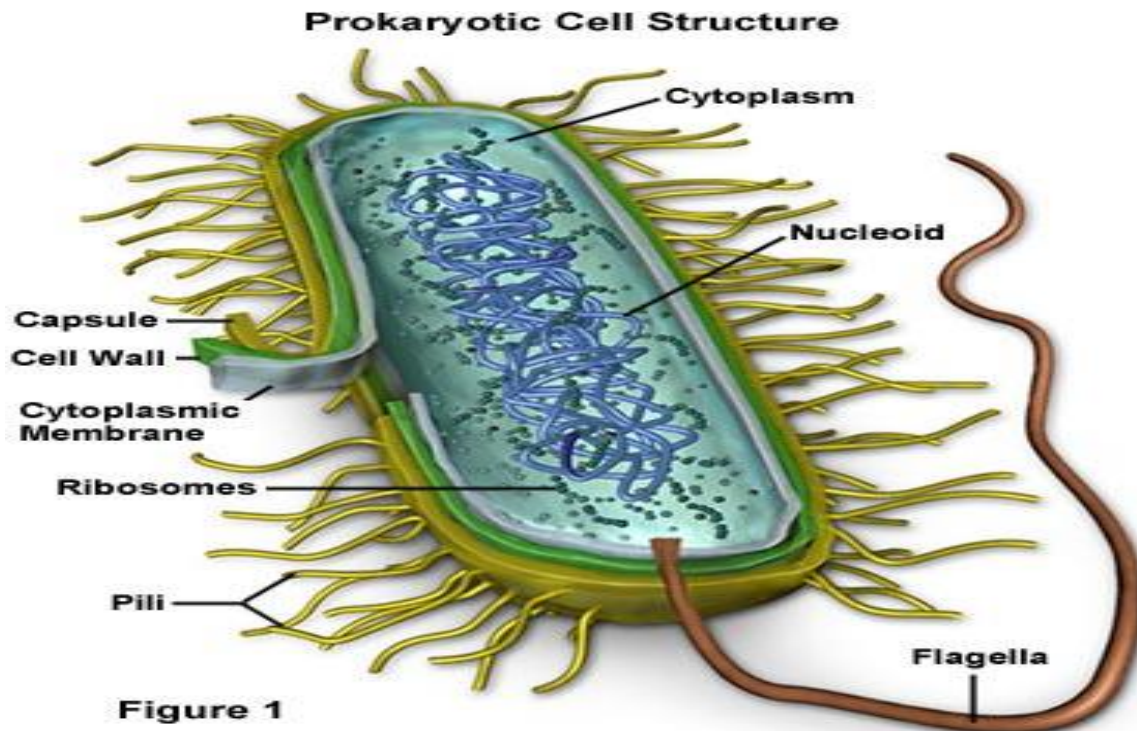
## CHEMOTHERAPY:

**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.

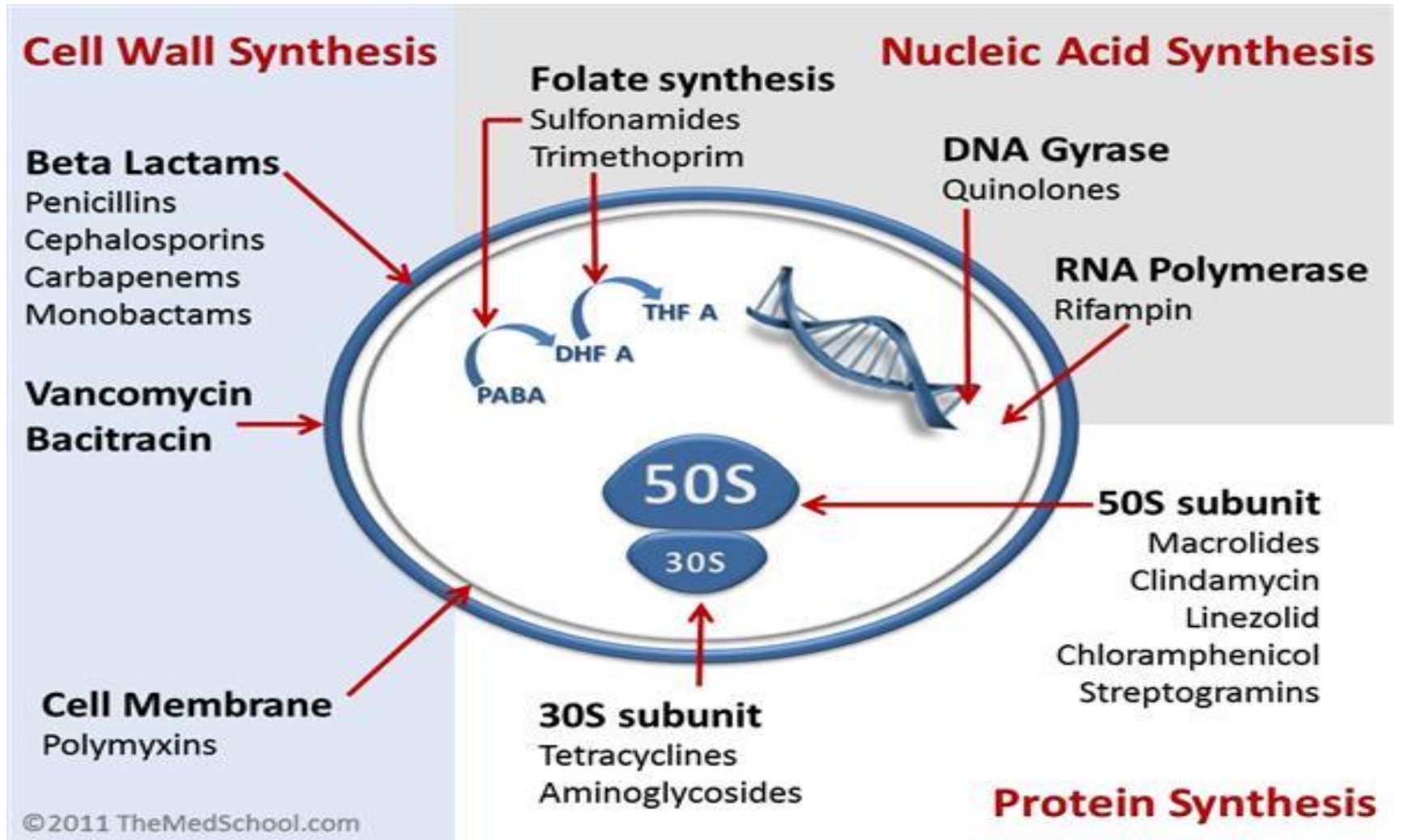
**Polymyxin B** : has the lowest therapeutic index and very toxic to human when given systemically.

# **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**

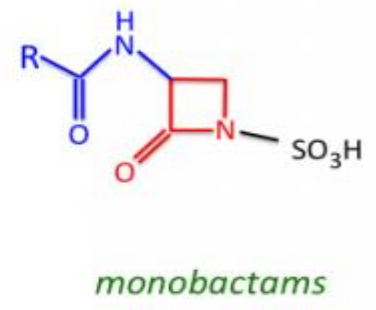
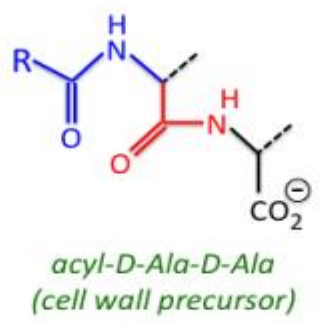
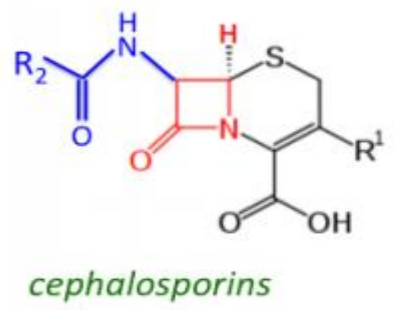
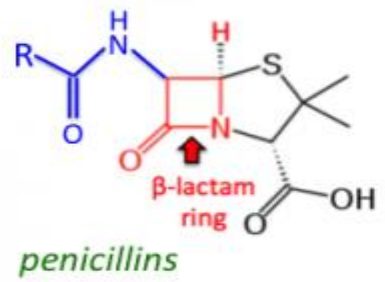
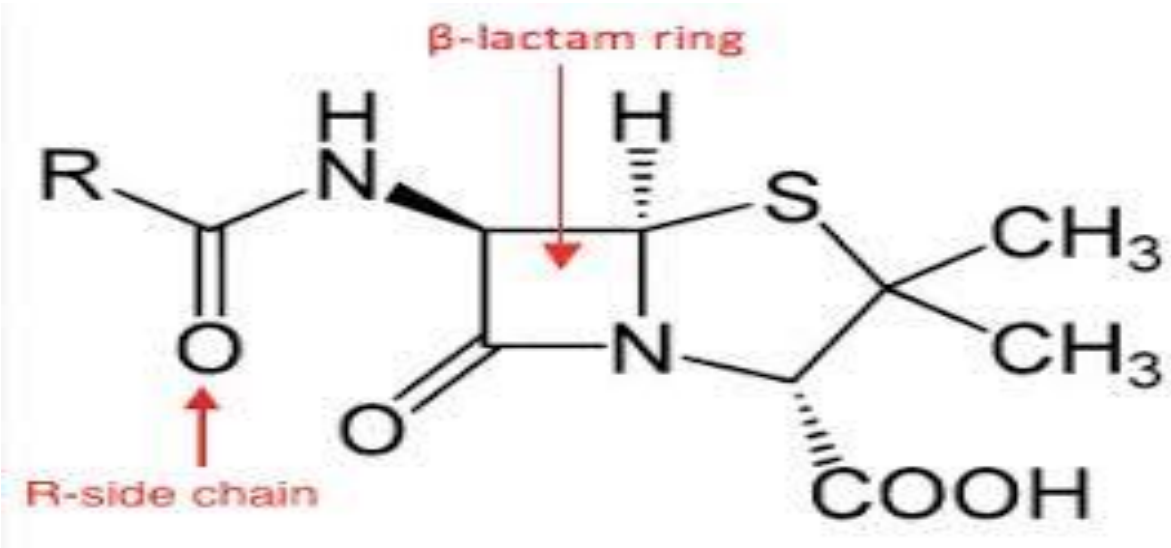
**Cephalosporins**

**Carbapenems**

**Monobactam**

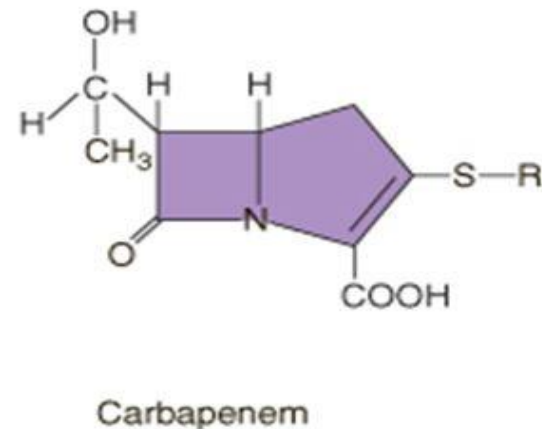
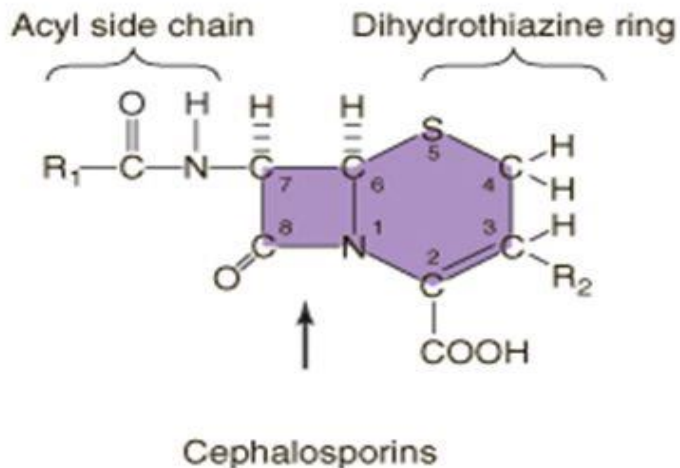
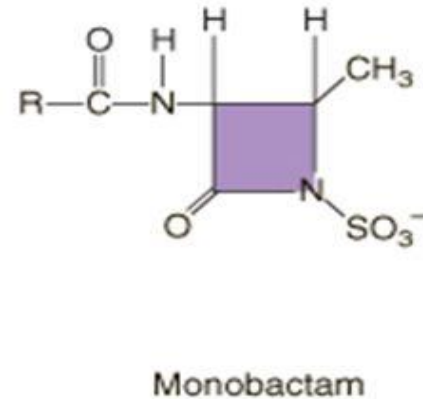
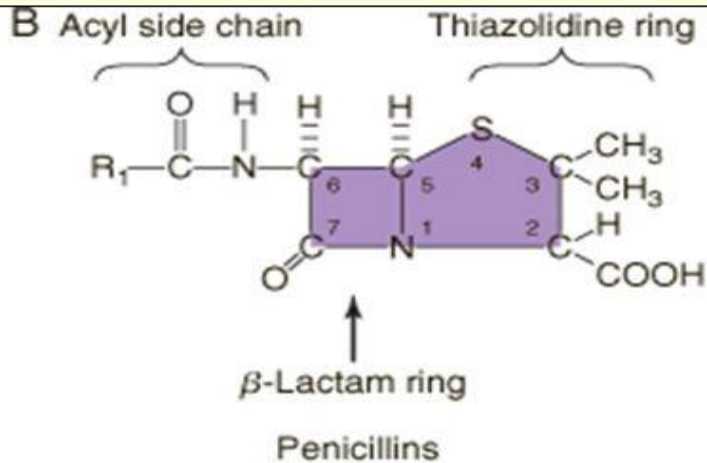
**Beta lactamase inhibitors**

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



# Beta-Lactam Antibiotics

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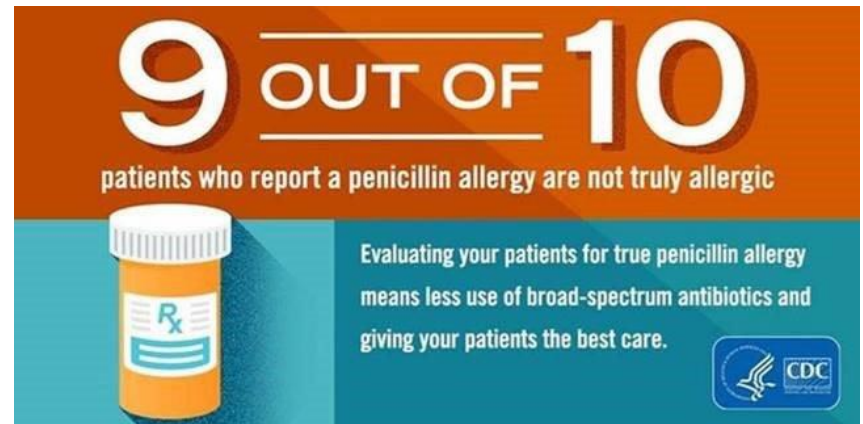


# $\beta$ - LACTAM ANTIBIOTICS

- 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.



**9 OUT OF 10**  
patients who report a penicillin allergy are not truly allergic

Evaluating your patients for true penicillin allergy means less use of broad-spectrum antibiotics and giving your patients the best care.



# 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**

# $\beta$ -Lactamase inhibitors

- $\beta$ -Lactams with limited antibacterial activity
- Irreversibly bind to  $\beta$ -lactamase enzyme
- Clavulanic acid, Sulbactam, Tazobactam
- Effective on Staph. Penicillinases and broad spectrum  $\beta$ -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, Campylobacter*, 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**

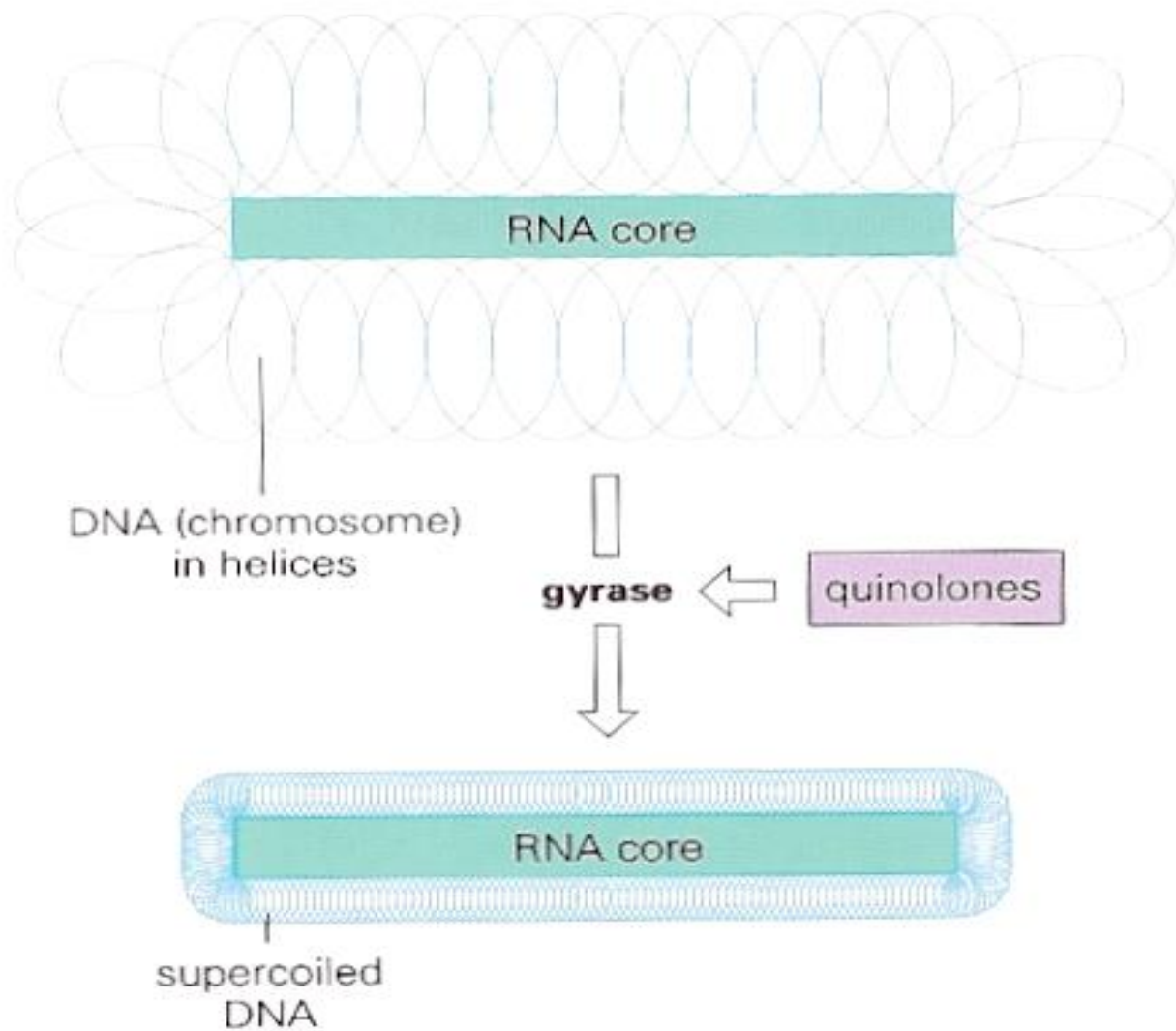
# RIFAMPICIN

- **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* x ← sulfonamides

**dihydropteroic acid**

↓

**dihydrofolic acid**

*dihydrofolate reductase* x ← 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 + Rifampicin for 4 months.

## Second line agents

- Streptomycin
- 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.

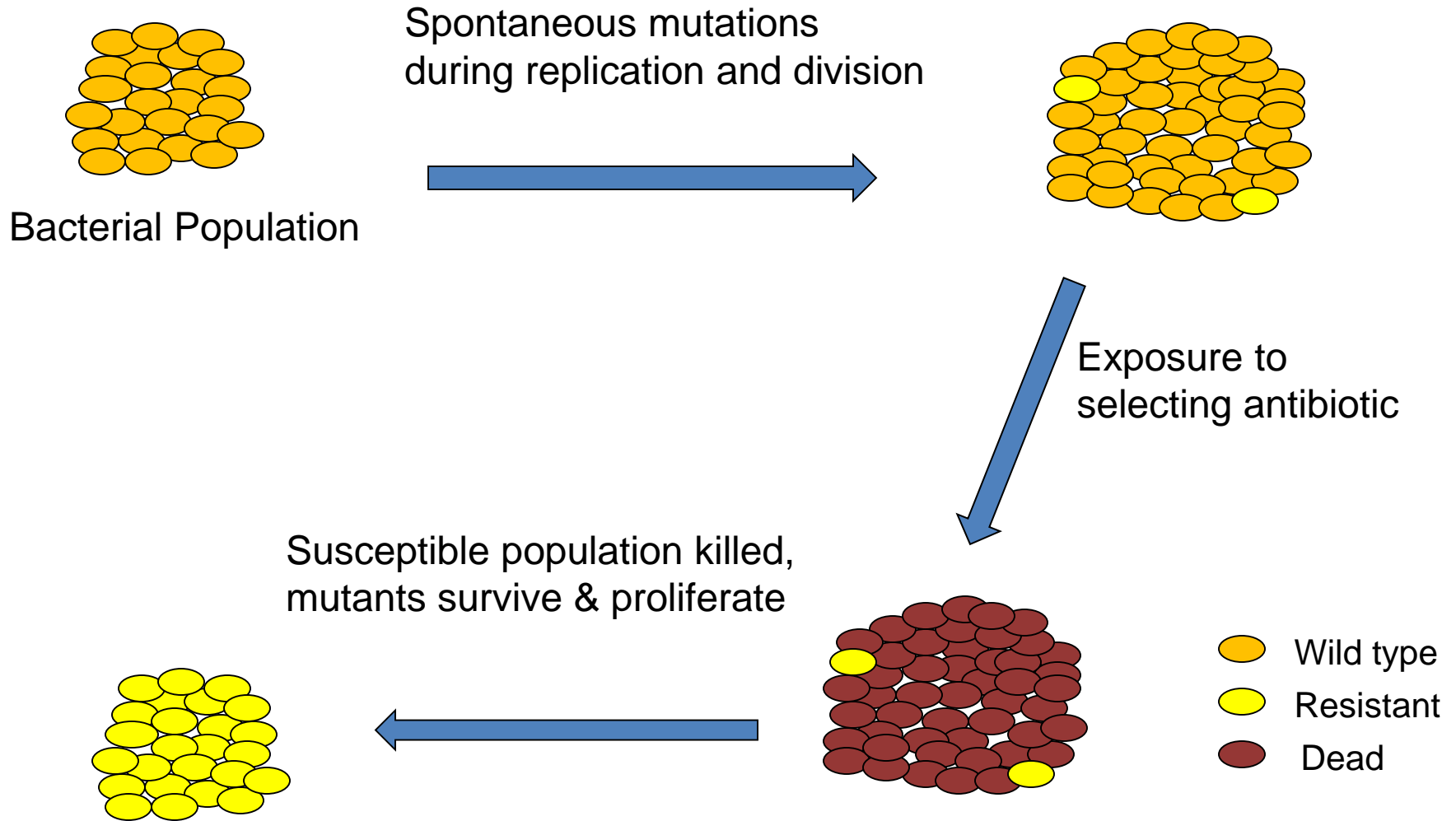
## Types of resistance:

**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)

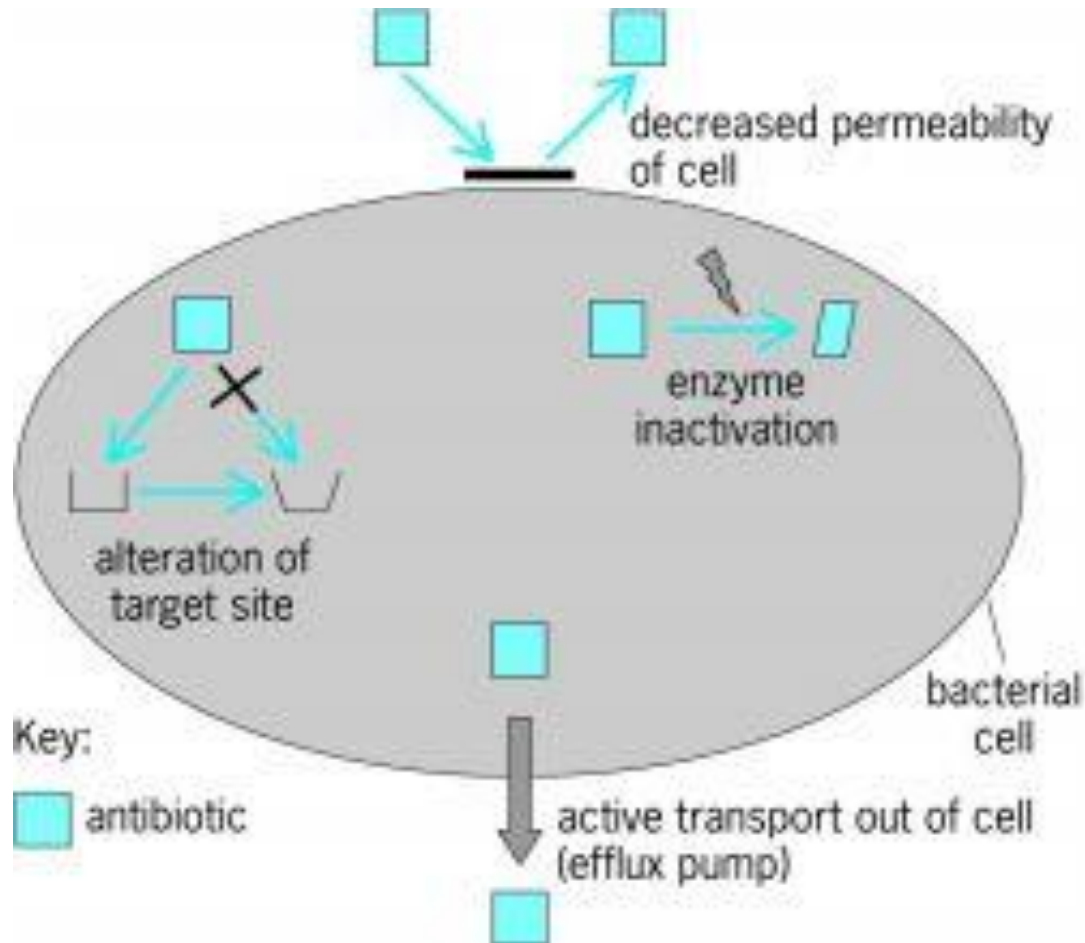
# Antimicrobial Selection of Resistance



# 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 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.**