



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
- Discuss mechanisms of resistance to antibiotics

Definitions/Terminologies

ANTIBIOTICS:

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

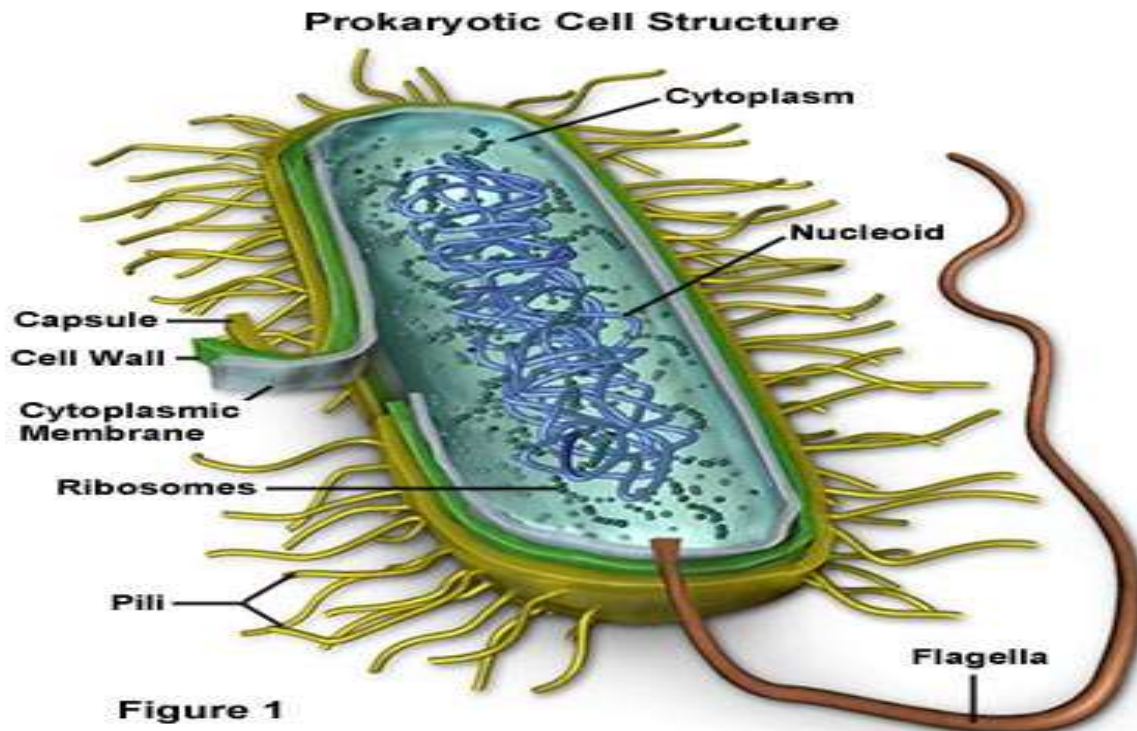
CHEMOTHERAPY:

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.

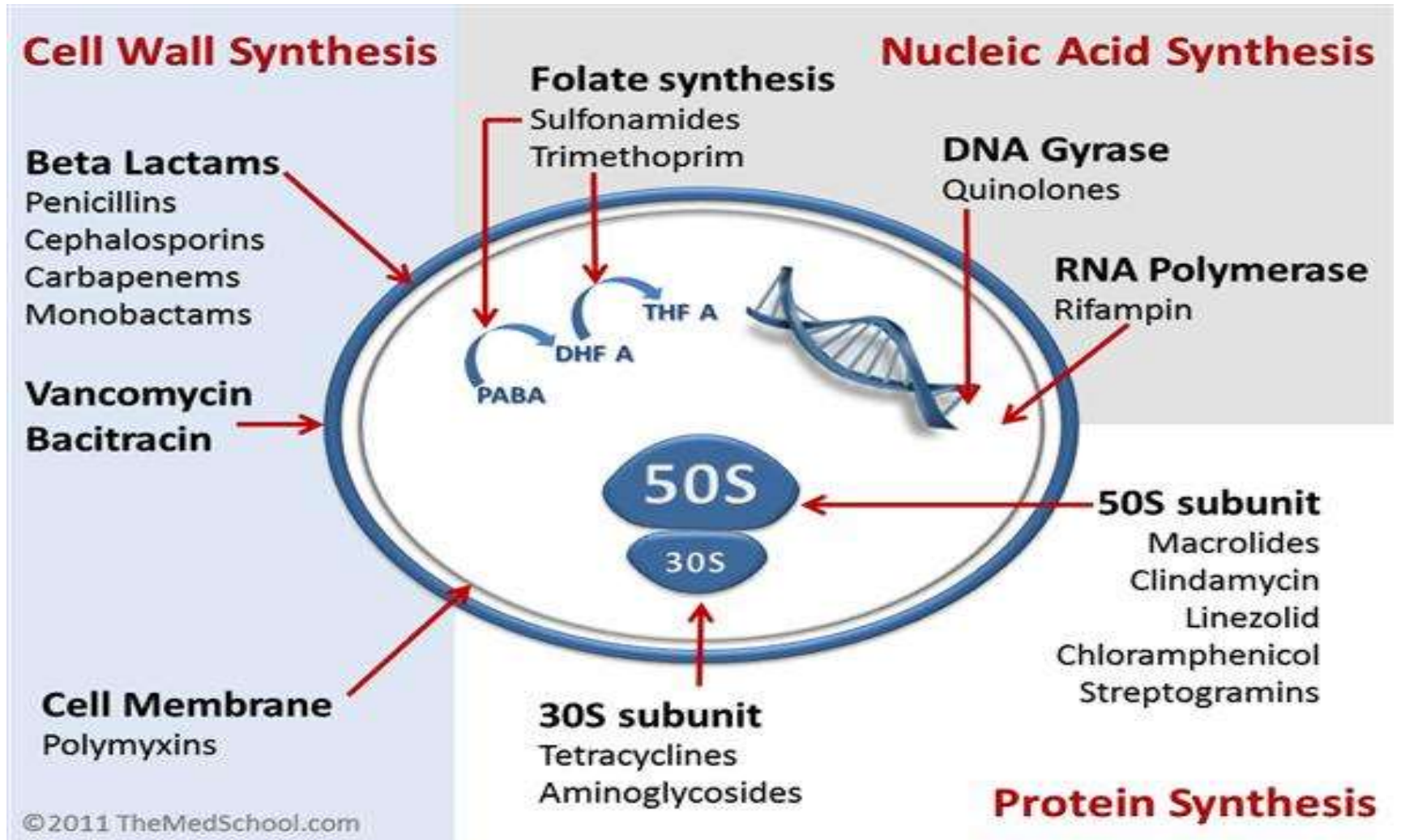
Aminoglycosides : has a low therapeutic index.

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

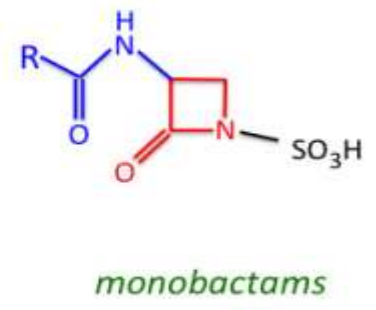
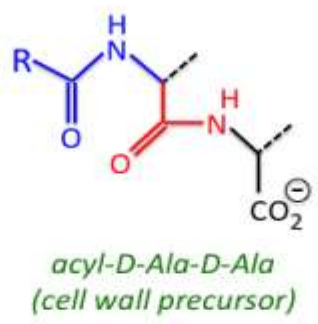
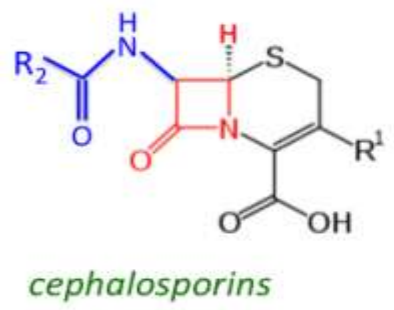
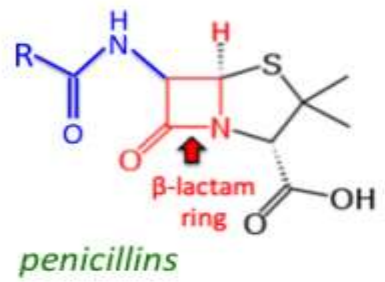
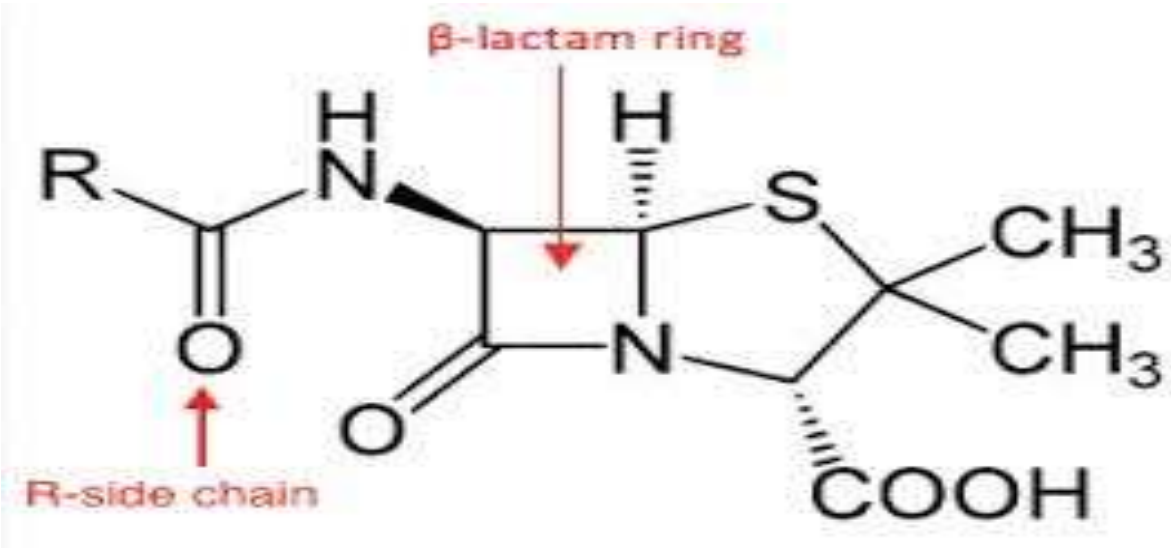
Cephalosporins

Carbapenems

Monobactam

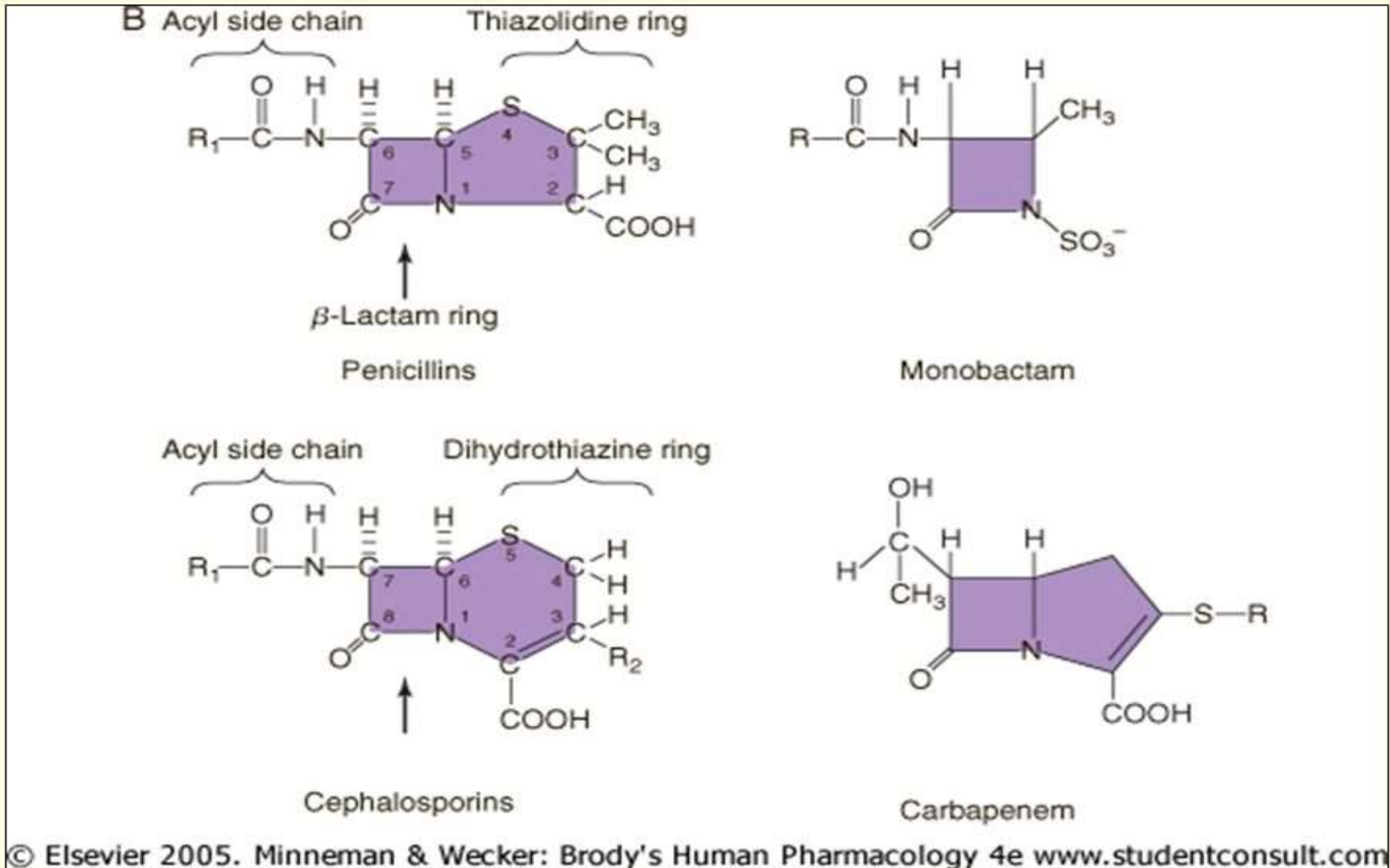
Beta lactamase inhibitors

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



Beta-Lactam Antibiotics

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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.



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.



The infographic features a large orange header with the text '9 OUT OF 10' in white, followed by 'patients who report a penicillin allergy are not truly allergic' in smaller white text. Below this is a teal section containing an illustration of an orange pill bottle with a white cap and a blue 'Rx' symbol. To the right of the bottle, the text reads 'Evaluating your patients for true penicillin allergy means less use of broad-spectrum antibiotics and giving your patients the best care.' The CDC logo is in the bottom right corner.

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**

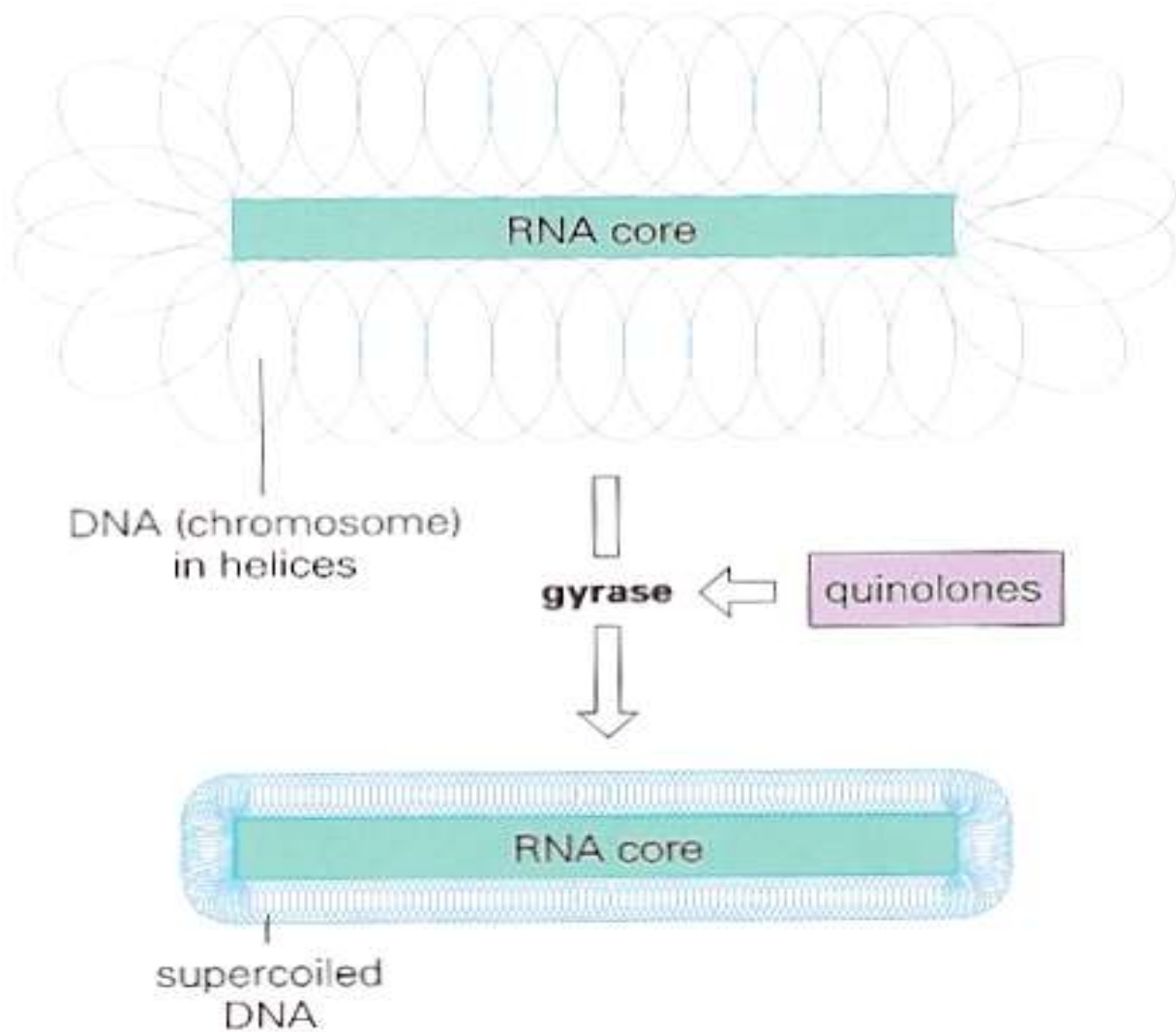
RIFAMPICIN

- **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 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.

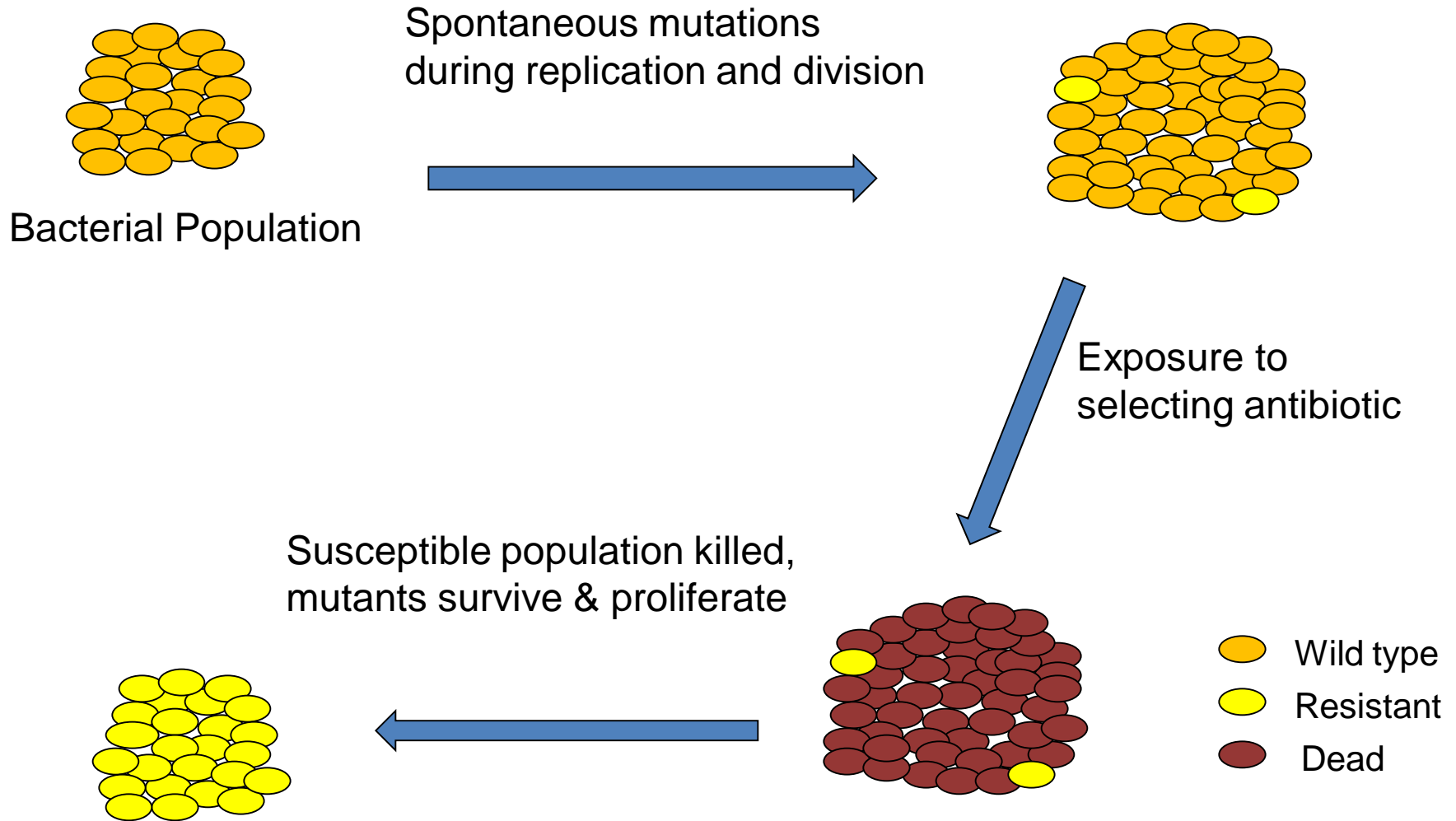
Types of resistance:

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)

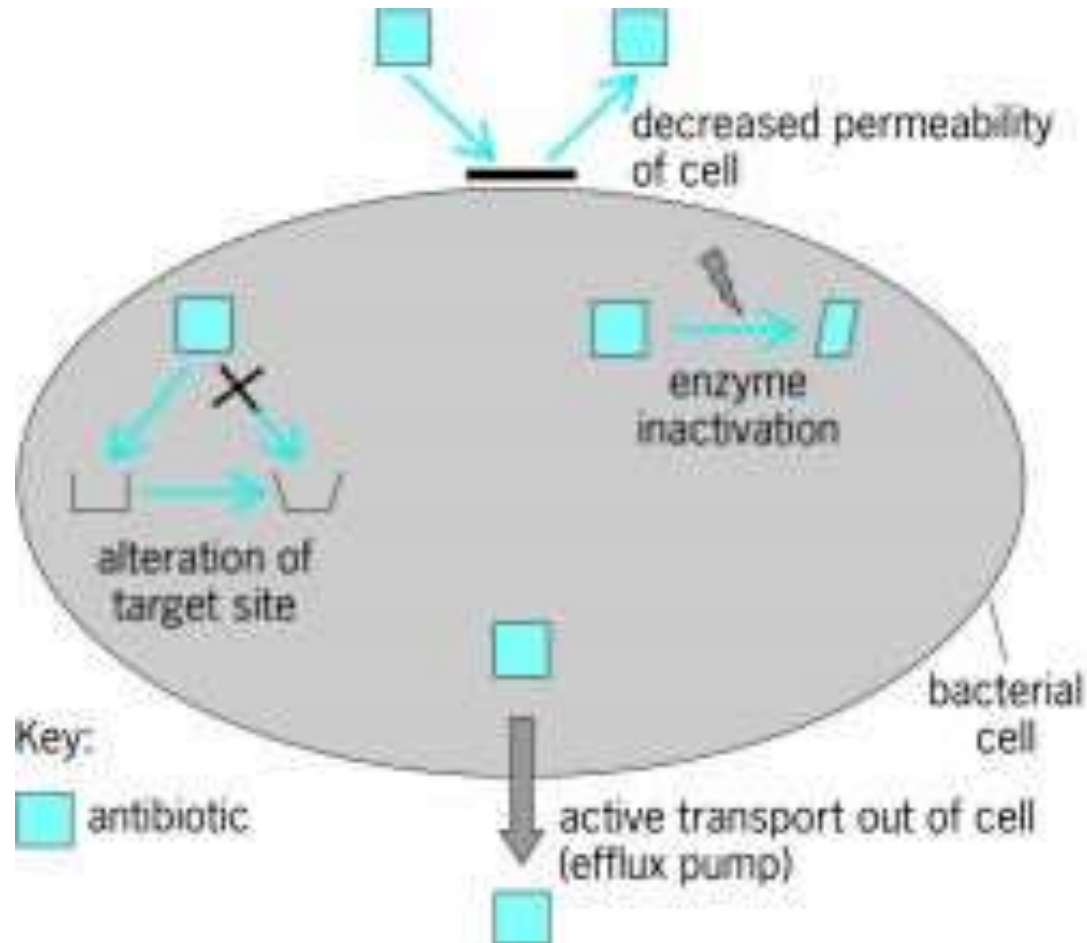
Antimicrobial Selection of Resistance



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
- PENETRATE 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.**