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ANTIBIOTICS
FOUNDATION BLOCK

ANTIMICROBIAL AGENTS

ANTIBIOTICS

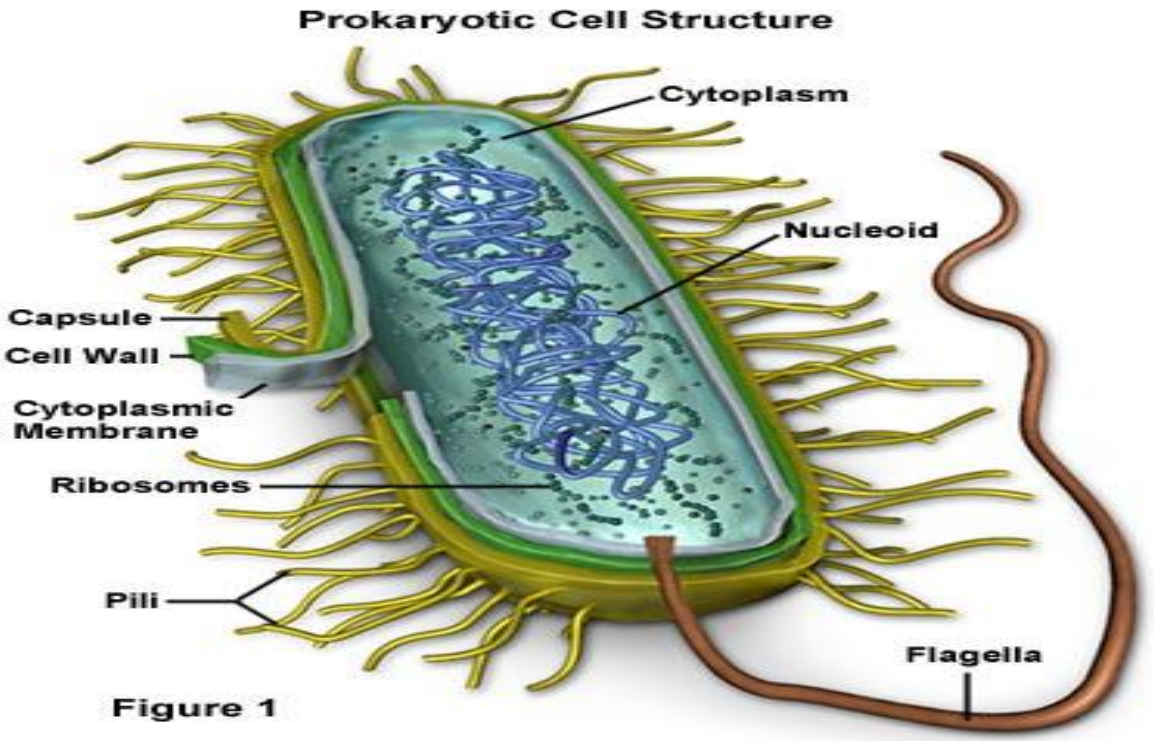
- Natural compounds produced by microorganism which inhibit the growth of other microorganism .

CHEMOTHERAPY

- Synthetic compounds .
- All together are **Antimicrobial Agents**.

SELECTIVE TOXICITY

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



***BACTERICIDAL*:** kills bacteria

***BACTERIOSTATIC* :** prevents multiplication.

Spectrum of activity

- **Broad spectrum** : affects Gram positive & Gram negative bacteria
- **Narrow spectrum** : affects selected organism.

THERAPEUTIC INDEX:

- The Ratio of Toxic dose to human / Therapeutic dose against bacteria.
- ***Examples:***

  Penicillin: High , is good to human.

  Aminoglycosides : low

  Polymyxin B : the lowest, is toxic to human.

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.**

ANTIMICROBIALS THAT INHIBIT CELL WALL SYNTHESIS

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

  Penicillins

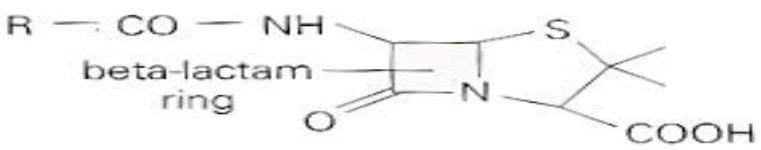
  Cephalosporins

  Carbapenems (imipenem & meropenem)

  Monobactam (aztreonam)

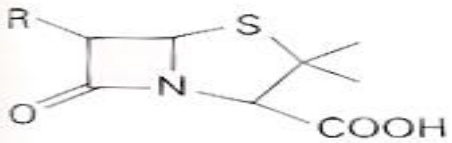
- **2- Vancomycin** (Teicoplanin)

THE BETA-LACTAM RING

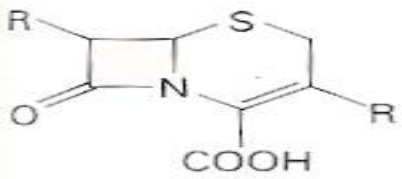


members ot the beta-lactam family

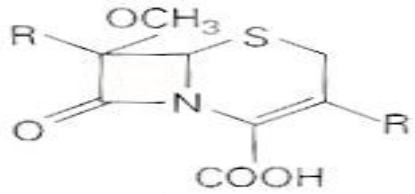
penicillins
e.g. benzyl penicillin, cloxacillin, flucloxacillin, ampicillin, amoxycillin, carbenicillin, ticarcillin, azlocillin, mezlocillin, piperacillin



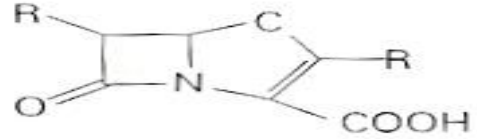
cephalosporins
e.g. cephalexin, cefaclor cefadroxil, cefuroxime cefamandole, cefotaxime ceftazidime



cephamycins
e.g. cefoxitin



carbapenems
e.g. imipenem



monobactams
e.g. aztreonam

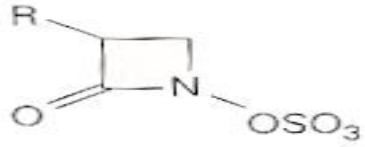


FIG. 1

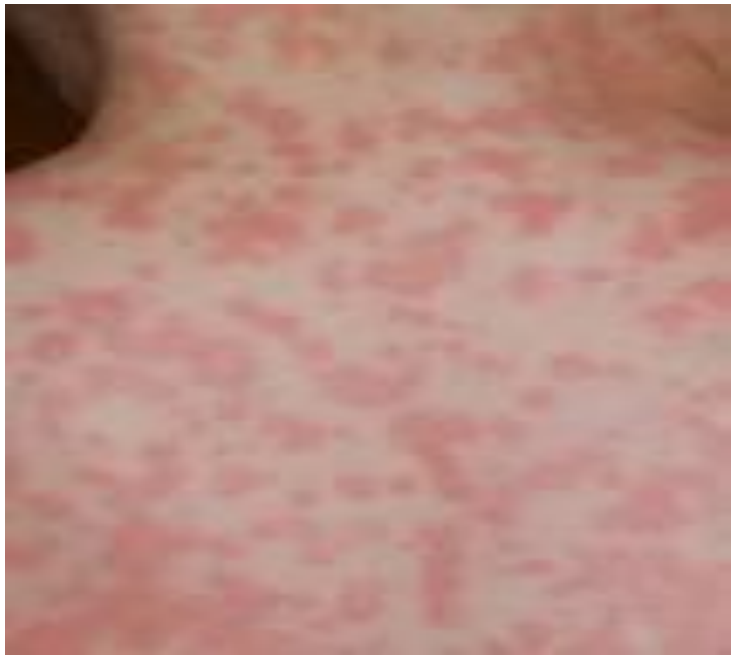
β - LACTAM ANTIBIOTICS

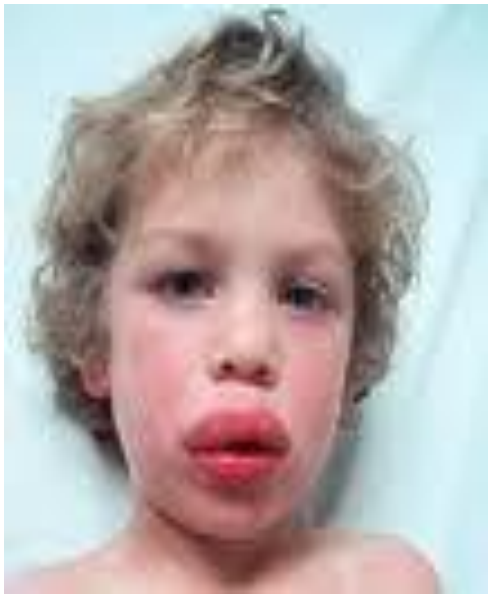
- Composed of : Beta- Lactam ring & Organic acid.
- Natural & Semi-synthetic
- Bactericidal
- Bind to penicillin binding protein (*PBP*)and interfere with trans-peptidation reaction.

Toxicity: mainly;

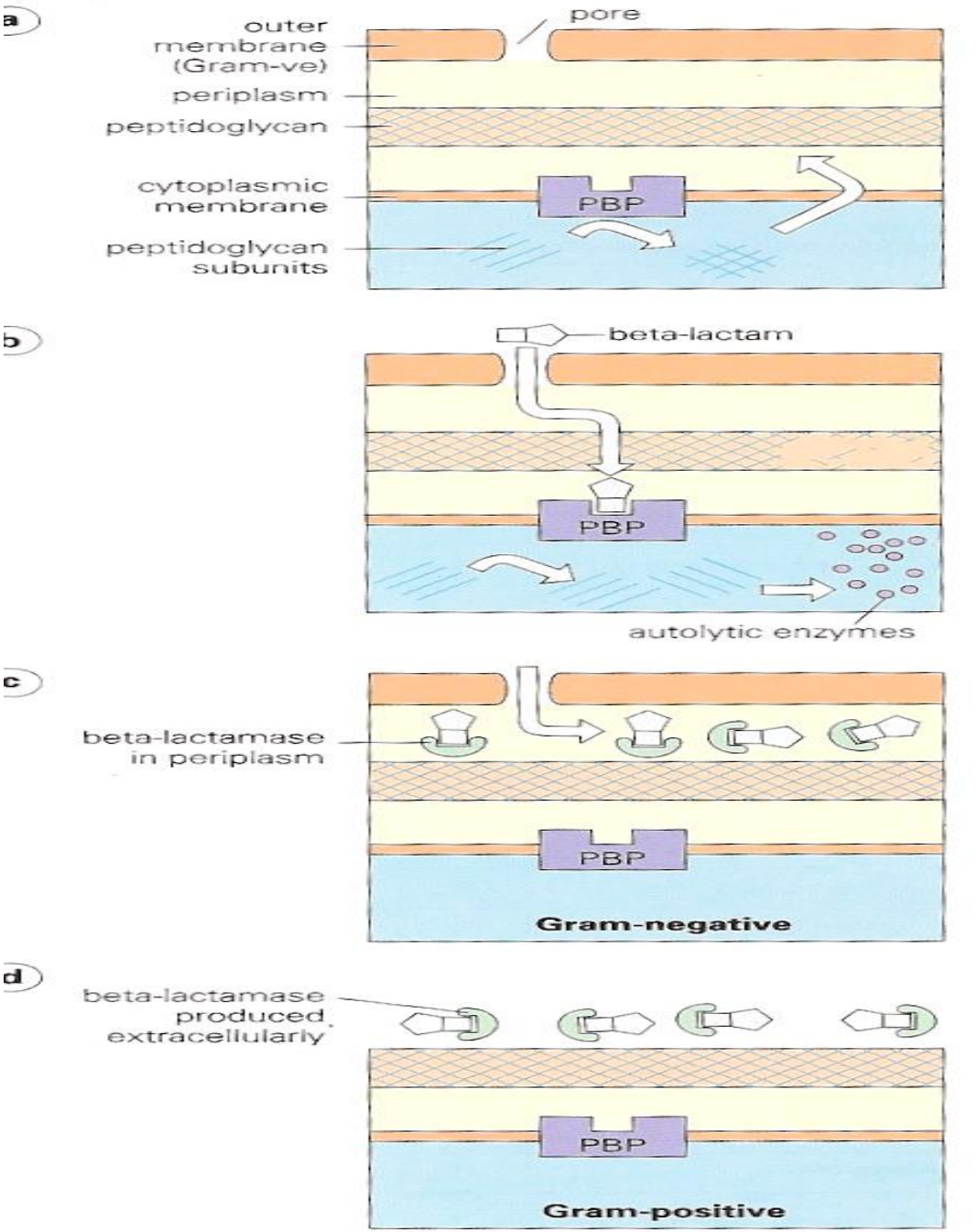
- Allergy ,common
- Anaphylaxis ,
- Diarrhea.

Allergy & Anaphylaxis





THE ACTION OF BETA-LACTAMS ON PBP FUNCTION



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**, mezlocillin-effective for *Pseudomonas.*

CEPHALOSPORINS

First Generation:

Cephradine

Ceohalexine

Second generation:

Cefuroxime

Cephamycin (Cefoxitin)

Third generation:

expanded spectrum

- eg. of third generation: Ceftriaxone
- Ceftazidime

Fourth generation:

- Cefepim
- Cefexime

VANCOMYCIN

- Glycopeptides, inhibit cell wall synthesis.
- Bactericidal . Acts on **Gram positive bacteria only (*narrow spectrum*)**.
- Given by **injection** only.
- Used for methicillin resistant *S.aureus* systemic infections (MRSA) , emperical treatment of Gram positive infections & pseudomembranous colitis.

- **Side effects:**

Red man syndrome , phlebitis, nephrotoxic & ototoxic.

ANTIBIOTICS THAT ALTER CELL MEMBRANES

- **Polymyxin B and Colistin**

- **Polymyxin B : a Peptide active against Gram negative bacteria only.**
- **Bactericidal.**
- **Only used *locally* due to serious nephrotoxicity when used systemically.**
- **Colistin used for the treatment of multi-resistant organisms (MRO) such as ;*Pseudomonas* and *Acinetobacter* infections.**

ANTIBIOTICS THAT INHIBIT PROTIEN SYNTHESIS

- **AMINOGLYCOSIDES**
- **TETRACYCLINES**
- **CHLORAMPHENICOL**
- **MACROLIDES**

AMINOGLYCOSIDES

- Bactericidal
- Acts only on Gram negative bacteria(*narrow spectrum*)
- Streptococci & anaerobes are naturally resistant
- Examples: Gentamicin ,Amikacin , Neomycin ,
- Given by injection .
- Side effects :Nephrotoxic & Ototoxic - dose related.

TETRACYCLINES

- Broad spectrum , bacteriostatic, not used for children under 8 yrs. or pregnant women. Oral absorption.
- Effective for Intracellular organisms eg. *Mycoplasma, Chlamydia ,Brucella* also for *V. cholera & Nocardia*

Classes

- Short acting: **Tetracycline**
- Long acting: **Minocycline , Doxycycline** (good CSF penetration).
- New tetracycline : **Tigycycline** *(covers MRSA,MSSA, some Gram negative bacteria and anaerobes.*
- **Side effects :**
- Permanent teeth discoloration , GIT disturbance

CHLORAMPHENICOL

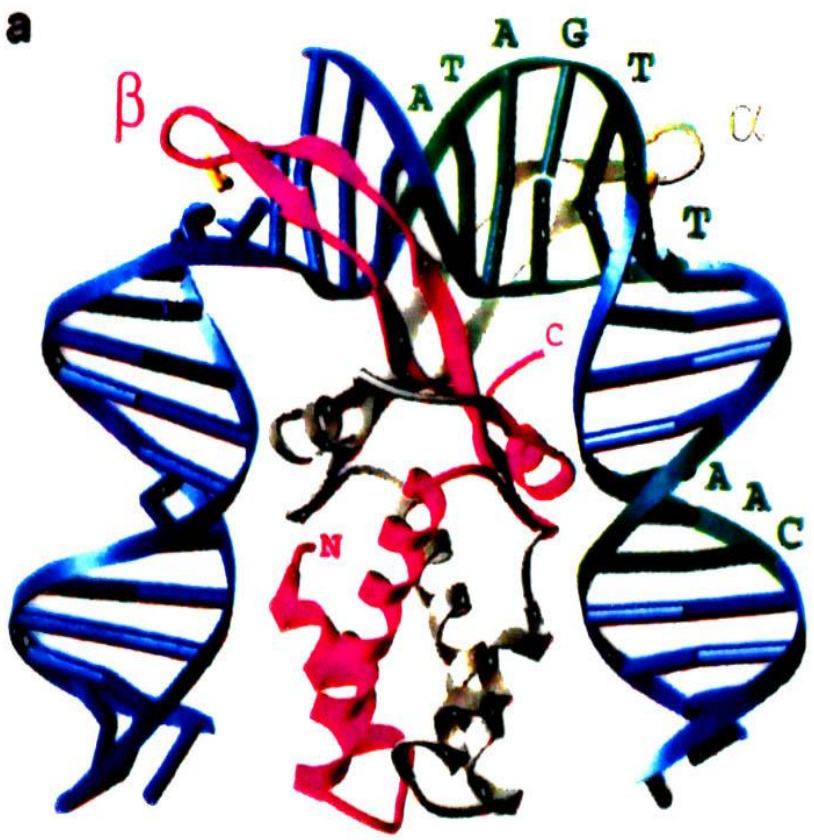
- Broad spectrum & bactericidal
- **Side effects : it affects bone marrow cells and cause aplastic anemia**
- Used only for severe infections not responding to treatment by other antimicrobials , also for the treatment of Rickettsial diseases.
- Used also *topically* for eye and ear infections.

MACROLIDES

- **Erythromycin & Clindamycin**
- Bacteriostatic
- **Good activity on :Legionella, Camylobacter, Gram negative and positive infections for patients allergic to Penicillins and Cephalosporins.**
- Clindamycin acts on **anaerobes** as well
- Side effects : GIT disturbance, Pseudomembraneous colitis (mainly *clindamycin*).
- **New Macrolides :**
- **Azithromycin & Clarithromycin** . Less side effects , better penetration and longer half life.

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
- Used in combination
- **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 cartilage (*animals*) & heart

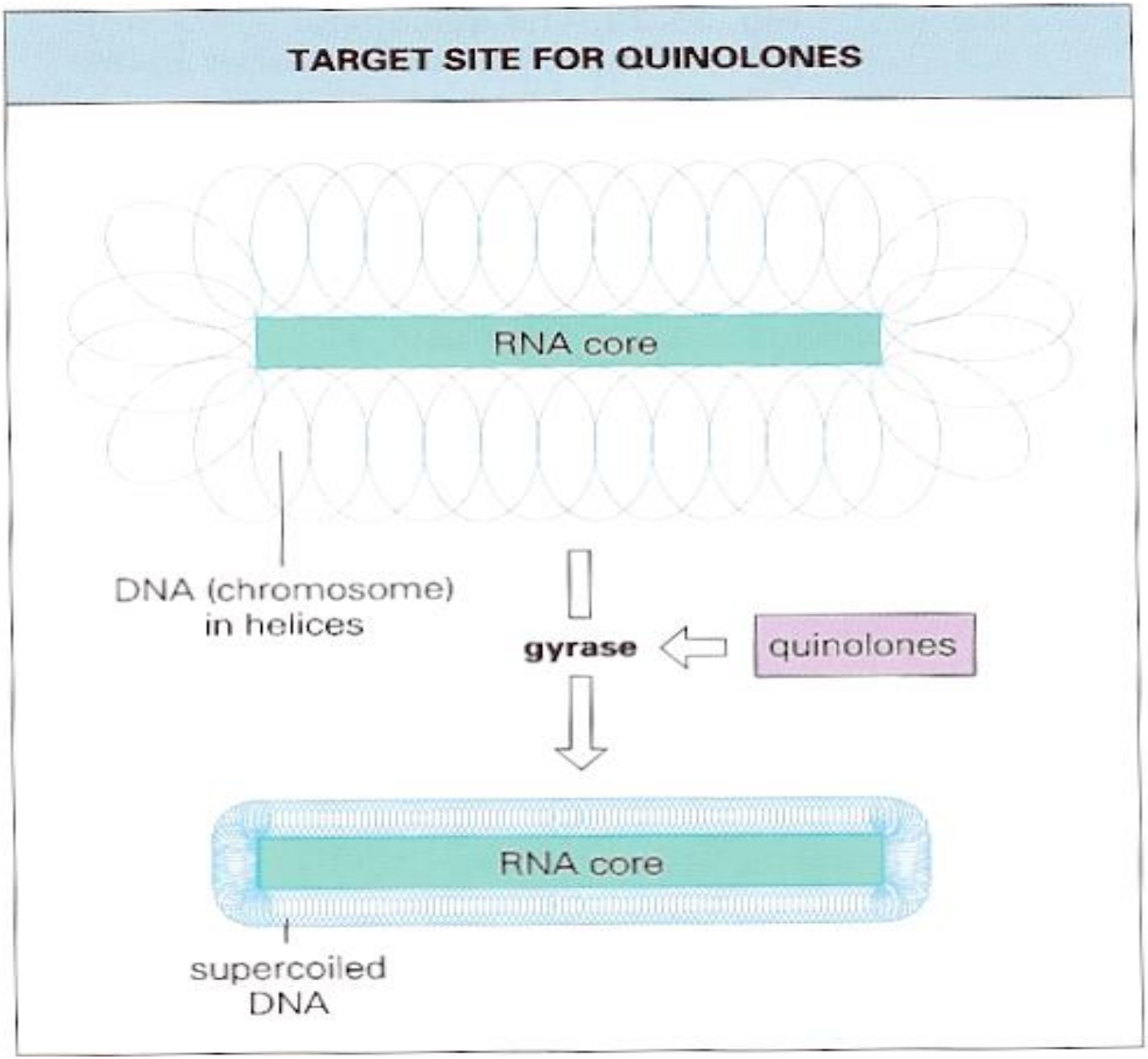

TARGET SITE FOR QUINOLONES
RNA core
DNA (chromosome)
in helices
gyrase
quinolones
RNA core
supercoiled
DNA

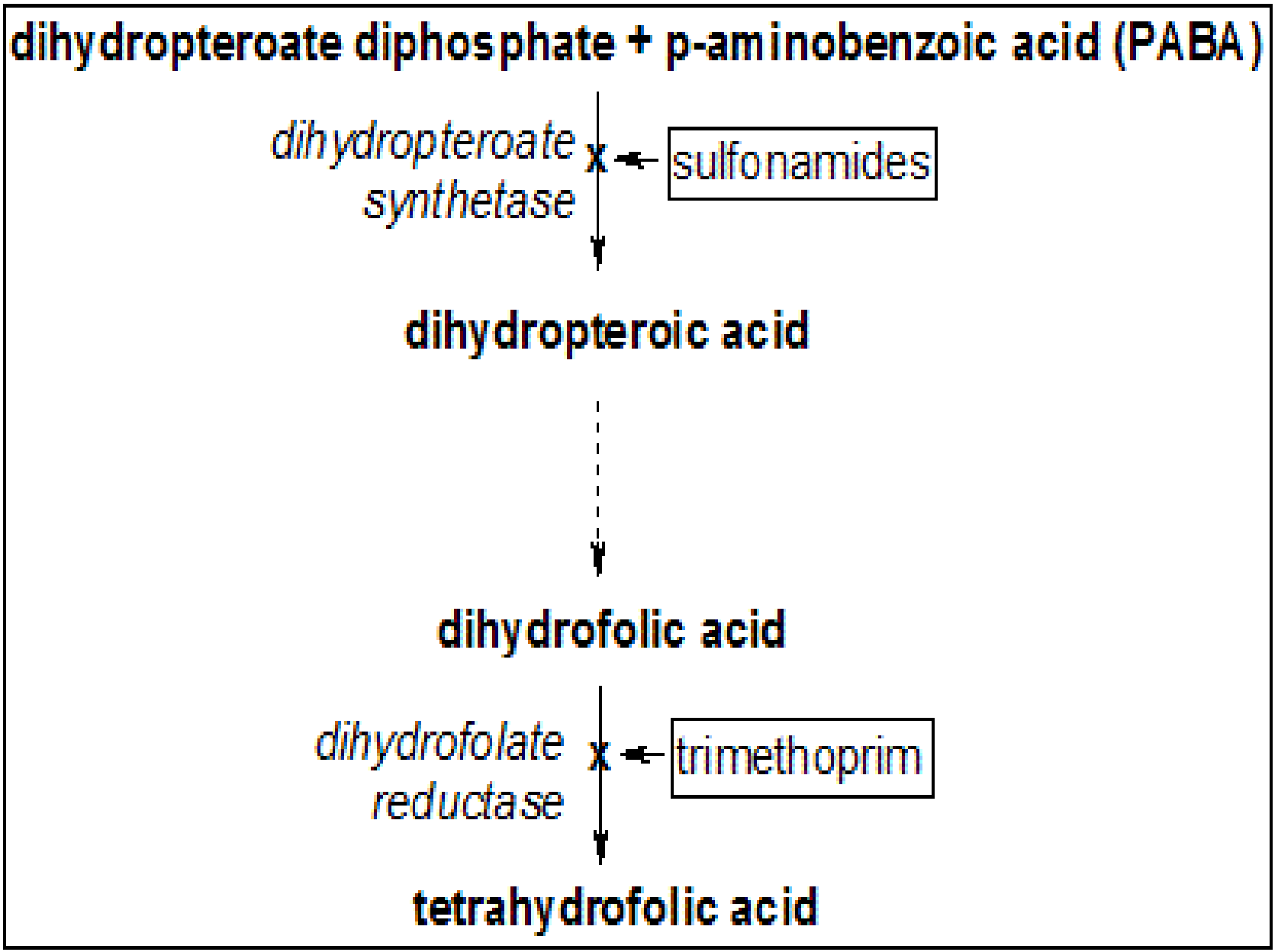
Fig. 3

Metronidazole

- 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 .**

ANTIMETABOLITES (folate inhibitors)

- **Trimethoprim-Sulfamethoxazole (TMP-SMX)**
- ***Combination of TMP-SMX called* : Bactrim / Septrin**
- **Block sequential steps in folic acid synthesis**
- **Effective of infections caused by *: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 4 drugs used for 6 months.

eg. INH+ Rifampicin + Ethambutol 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.

Isoniazid (INH)

- **Bactericidal**
- **Affects mycobacteria at different sites of the lung tissues.**
- **Used for the treatment and prophylaxis of tuberculosis.**
- **Side effects: peripheral neuritis &liver toxicity**

- **Ethambutol**

Bactericidal

Concentrated in the phagolysosomes of alveoli

Side effect: optic neuritis

- **Pyrazinamide**

Acts on acid environment of macrophages

Side effects: hepatitis and arthralgia

ANTIBIOTIC RESISTANCE IN BACTERIA

- DUE TO INDISCRIMINATE USE OF ANTIMICROBIALS
- **SELECTIVE ADVANTAGE OF ANTIBIOTICS**

TYPES OF RESISTANCE

PRIMARY:

- **Innate resistance** **eg. *Streptococcus* & anaerobes are naturally resistant to gentamicin.**

ANTIBIOTIC RESISTANCE IN BACTERIA (Continue)

Acquired resistance ,due to :

- 1- **MUTATION**: ***Mycobacterium tuberculosis*** **resistant to streptomycin**
- 2- **GENE TRANSFER**: **plasmid mediated or through transposons**

Cross resistance :

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

eg. resistance to erythromycin and clindamycin

Dissociate resistance:

- **eg. resistance to gentamicin does not confer resistance to tobramicin .**

MECHANISMS OR RESISTANCE

1- Permeability changed

2- Modification of site of action, eg. Mutation.

3- Inactivation by enzymes . eg. Beta- Lactamase & aminoglycoside inactivating enzymes

4- Passing blocked metabolic reaction eg. *PABA (para amino benzoic acid)* → folic acid , and is plasmid mediated.

PRINCIPLES OF ANTIMICROBIAL THERAPY

- INDICATION
- CHOICE OF DRUG
- ROUTE
- DOSAGE
- DURATION
- DISTRIBUTION
- EXCRETION
- TOXICITY
- COMBINATION USE AS IN TUBERCULOSIS
- PROPHYLAXIS:

Prophylaxis
SHORT TERM:

- MENINGITIS

LONG TERM:

- Tuberculosis, Recurrent urinary tract infections , Rheumatic fever

Criteria for ideal antimicrobial agent

- Has selective toxicity
- Causes no hypersensitivity
- Penetrate tissues quickly
- Resistance does not develop quickly
- Has no effect of normal flora
- Broad spectrum

Take home message

- **Antibiotics can do harm ,develop resistance so must be used judiciously.**
- **Antibiotics potentiate the function of human immune system to fight microbes.**
- **We must know the toxicity , pharmacokinetics, spectrum of activity of antimicrobials to make best guess of use.**