# Introduction

**Definition of chemotherapy:**

The use of synthetic chemicals to destroy the infective agents.

**Definition of antibiotic:**

Chemical substance produced by living microorganism that destroys or suppresses the growth of another microorganism.

**Selective toxicity:**

- Ideal antibiotic show selective toxicity, this means that the agent must produce toxic effect on the organism at concentration tolerated by the host.
- This selective toxicity depends on the presence of biochemical differences between the parasite and the host.

- These agents may by:

- Bacteriostatic: inhibit growth of microorganism as tetracyclines, sulfonamids.
- Bactericidal: cause death of the microorganism as penicillins, cephalosporins.

## Classification of chemotherapeutic agents:

a) Antimicrobial: antibacterial, antiviral, antifungal.

b) Antiparasitic: anthelmintic, antiprotozoal.

c) Antineoplastic.

## Classification of antibacterial agents:

I. **According to their spectrum against bacteria:**

a. Drugs act mostly against gram positive organisms:

- β-lactam antibiotics, erythromycin, vancomycin

b. Drugs act mostly against gram negative organisms:

- Aminoglycosides, polymyxins.

c. Drugs act against gram positive and gram negative organisms ;

- Chloramphenicol, tetracyclines.

II. **According to mechanisms of action:**

A. Inhibition of bacterial cell wall synthesis:

▶Act by impairing the synthesis of peptidoglycan which has great strength and provide bacterial surface with rigidity necessary to protect the underlying cytoplasmic membrane from osmotic shock.

- Impair in structure or synthesis of this peptidoglycan → damage of cytoplasmic membrane → cell lysis (bactericidal action).
- Peptidoglycan is specific to bacterial cell so its inhibition is highly selective
- Examples of drugs act by this mechanism:

▶penicillins, cephalosporins, bacitracin, cycloserine, vancomycin, INH

B. Inhibition of the function of cytoplasmic membrane:

- Cytoplasmic membrane acts as an osmotic barrier and as a medium for selective transport of nutrient into the bacterial cell.
- Drugs may cause ↑ in the permeability of the cytoplasmic membrane and disturbance in its function → macromolecules, ions escape from the cell → cell damage & death.
- Selective activity against cell membrane is present as antibiotics bind to certain substance present only in organisms.
- Examples of drugs act by this mechanism: amphotericin B, polymyxins, nystatin, azoles.

C. Inhibition of some metabolic process:

1. Competition for an essential metabolite:

- As in sulfonamides (bacteriostatic) which compete with P-aminobenzoic acid for the bacterial enzyme.
- This bacterial enzyme converts P-aminobenzoic acid to folic acid.

2. Inhibition of protein synthesis:

- Act by inhibition of subunits of bacterial ribosomes which responsible for synthesis of protein.
- Have mild effect on mammalian ribosomes as they differ from bacterial ribosomes.
- Examples of drugs act by inhibition of protein synthesis:

- Drugs bind with 30S subunit of ribosomes: aminoglycosides, tetracyclines.
- Drugs bind with 50S subunit of ribosomes: chloramphenicol, clindamycin, macrolides (as erythromycin).

1. Inhibition of nucleic acid synthesis: (DNA, RNA)

- Quinolones, fluoroquinolones → inhibit DNA gyrase enzyme.
- Rifampin → inhibits RNA synthesis by inhibition of DNA-dependent RNA polymerase.
- Actinomycins, sulfonamides, trimethoprim → inhibit DNA synthesis.

III. **According to the ultimate fate of the organisms:**

a) Bacteriostatic drugs:

- Drugs which temporarily inhibit the growth of microorganism as tetracyclines, sulfonamides, chloramphenicol.

b) Bactericidal drugs:

- Drugs that cause death of microorganism as penicillins, cephalosporins, aminoglycosides

➢ This classification is not absolute; as it depends on the concentration of the antibiotic and the microorganism as:

- Erythromycin is bactericidal only in high concentrations.
- Chloramphenicol is a bacteriostatic drug, but may be bactericidal to certain species as H. influenza, N. meningitidis.

➢ When a bacteriostatic drug is used the defense mechanism of the host (humoral or cellular immunity) must be able to destroy the organism whose multiplication is stopped by the drug.

➢ In cases of infections that cannot be controlled by host defense mechanisms (as in infective endocarditis) or when the immune system is compromised (as by diseases or drugs), bactericidal drugs should be used.

## ▶Clinical uses of antibiotics:

▶- In treatment of infection:

- ✓ Not used in undiagnosed infection, but need identification of the organism using blood culture.
- ✓ In cases of severe infection we can use empirical treatment.

## ▶Resistance to antibacterial agents:

▶a) Mechanism of resistance:

1. Production of enzyme that destroy file active drug:

- Penicillinase enzyme for penicillins.
- Adenylase, acetylase. phosphorylase for aminoglycosides.
- Acetyl transferase for chloramphenicol.

2. Change in permeability of the microorganism to drugs:

as in aminoglycosides, tetracyclines, polymyxins

▶This can be overcome by the simultaneous use of cell wall active drug as penicillins.

3. Microorganisms develop a modification of target enzyme or drug receptors as in case of sulfonamides, the bacterial enzyme lose its affinity for the drug while retaining its affinity for its substrate (PABA).
4. Microorganisms remain metabolically inactive. As active replication of bacteria is needed for most antibacterial drug action, So inactive bacteria → resist the action of antibiotics

- Their offspring are fully susceptible.
- As in mycobacteria which survive in tissues for many years and don't multiply.
- But if the organism started to multiply (as after corticosteroid therapy) it becomes full susceptible to the same drug.

## b) Genetic determinants of antibiotic resistance:

1. Chromosomal determinants

- For most organisms resistance due to chromosomal mutation is not of great clinical significance.

- as spontaneous mutation rate for any particular gene is very low in bacterial population (about $1 / 10^6 - 10^8$).

2. Extrachromosomal determinants: (plasmids):

- Due to extrachromosomal genetic elements present in cytoplasm called plasmids.

- Type of plasmids that carry genes for resistance to antibiotics called R- plasmid.

- Plasmids are circular DNA molecules weighting 1-3% of weight of chromosome.

## c) Transfer of resistance genes:

1. Between genetic elements within the bacterium

- From plasmid to another, from plasmid to chromosome and vice versa.

2. Between bacteria

- from one bacteria into another of the same or different species.

- Of great importance in spread of resistance to antibiotics.

## d) Methods of transfer of resistance genes:

### 1. Conjugation

- Transfer of genetic material from one bacteria to another during cell to cell contact (mating), bacteria may be of the same or different species.
- Main mechanism for spread of resistance

### 2. Transduction

- Plasmid DNA is enclosed in bacterial virus (bacteriophage) and transferred by the virus to another bacteria of the same species.

### 3. Transformation:

- Plasmid DNA is enclosed from one bacteria to the environment to be taken by another one and incorporated in its genome.
- Recombinant DNA technology is an example of transformation.

### 4. Transposition

- An exchange of short DNA sequences (transposons) which carry few genes, occurs between one plasmid and another or between a plasmid and part of chromosome within a bacterial cell.

Adverse reactions of antibacterial agents:

1. Toxic reactions.
2. Hypersensitivity reaction.
3. Superinfection:

- Occur with broad spectrum antibiotics or combination of antibiotics as they cause inhibition of normal flora in intestinal, upper respiratory, genitourinary tracts.
- This may lead to dangerous infection by enterobacteriaceae, pseudomonas or Candida which may be difficult to treat.

## MAIN ADVERSE EFFECTS OF ANTIBIOTICS

- Beta-lactams: allergic reaction (skin rash→ anaphylaxis).
- Ampicillin, amoxicillin: diarrhea.
- Clindamycin: diarrhea (colitis).
- Aminoglycosides: nephrotoxicity, ototoxicity, neuromuscular paralysis.
- Vancomycin: nephrotoxicity, ototoxicity.
- Chloramphenicol: B.M. depression, gray baby syndrome, GIT
- Tetracyclines: GIT, hepatic & renal toxicity, teeth & bone deposition or discoloration, vestibular toxicity.
- Erythromycin: GIT, cholestatic jaundice, ototoxicity.
- Sulfonamides: GIT, hypersensitivity, crystalluria, BM depression.

## Combinations of antimicrobial agents

### a) Indications (advantages)

1 - Treatment of mixed bacterial infections as in:

intra-abdominal infection, hepatic and brain abscesses, genital infections.

2- Therapy of severe infections in which a specific cause is unknown.

3- Prevention of development of resistant microorganisms as in treatment of T.B.

4- Enhancement of antibacterial activity in treatment of specific infections and may produce synergistic effect which leads to:

- Reduction of the dose of one or both.
- Rapid or complete bactericidal effect which not achieved with either drug alone.

### b) Examples of synergistic combinations:

1- Aminoglycosides + beta-lactam antibiotics in treatment of enterococcal endocarditis, pseudomonas infection.

2- Sulfonamides + trimethoprim in treatment of infections resistant to sulfonamides alone.

3- Beta-lactamase inhibitors (clavulanic, sulbactam) + beta-lactam antibiotics (amoxicillin, ampicillin) in treatment of organism producing beta-lactamase as H. influenza.

## c) Disadvantages:

1- Risk of toxicity from two or more agents.

2- Increased cost.

3- Antagonism of antibacterial effect if bacteriostatic is combined with bactericidal agent, as in treatment of pneumococcal meningitis by penicillin, , the effect is better than if penicillin is combined with chlortetracycline.

4- May ↑bacterial resistance.

## Failure of antibiotic therapy (misuses of antibiotic):

1. Treatment of non-bacterial disease (misdiagnosis) as in treatment of viral infection by antibiotic.
2. Treatment of fever of undetermined origin.
3. Improper dosage.
4. Improper choice of antibacterial agent as use of bacteriostatic in cases where bactericidal agent is needed i.e. endocarditis.
5. Omission of surgical drainage for purulent exudate (pus) or necrotic or avascular tissues.

## Prophylactic use of antibiotics (chemoprophylaxis):

1- To protect healthy persons from invasion by specific microorganism to which they are exposed.

As the use of penicillin G to prevent infection with group A Streptococci or Gonorrhea after contact with infected person.

2- To prevent secondary bacterial infection in patients who are at high risk.

As in patients receive cancer chemotherapy or having organ transplantation.

3- To prevent endocarditis in patients with valvular or cardiac lesion who are undergoing dental or surgical procedures that produce high risk of bacteremia.

4- The use of antibiotic after surgical operation is controversial however we need to use it in selected cases as:

- In dirty and contaminated operation as surgery of GIT.
- In operation need insertion of prosthetic implants as prosthetic heart valves or artificial orthopedic devices where the complications of infection are so dangerous.

# Sulfonamides

I. **Classification of sulfonamides:**

1. Drugs absorbed rapidly and excreted rapidly:

   - sulfisoxazole, sulfadiazine, sulfamethoxazole.

2. Drugs absorbed very poorly when used orally, so active in bowel lumen:

   - sulfasalazine (sulfapyridine + 5-aminosalicylate).

3. Drugs used mainly for topical use:

   - sulfacetamide, mafenide, silver sulfadiazine.

4. Drugs absorbed rapidly and excreted slowly (long acting), more toxic:

   - sulfadoxine (long acting due to high protein bind, extensive tubular reabsorption).

II. **Mechanism of action:**

**P-Aminobenzoic acid (**PABA) $\xrightarrow{\text{Dihydropteroate synthetase}}$ **dihydrofolic acid**

$\xrightarrow{\text{dihydrofolate reductase}}$ **Tetrahydrofolic acid → purine → DNA**

- Sulfonamides act by competitive inhibition of dihydropteroate synthetase enzyme which converts PABA to dihydrofolic acid.
- Trimethoprim causes inhibition of dihydrofolate reductase.
- Human not affected by sulfonamides as human cannot synthesize folic acid inside the body and use preformed folic acid (due to lack of enzymes of folate pathway).
- Sulfonamides are mainly bacteriostatic.

3. **Pharmacokinetics:**

- Except sulfasalazine, all sulfonamides are rapid absorbed from GIT.
- Bind to P.P. (20-90%).
- Widely distributed to all tissues & body fluids.
- Can pass placental barrier.
- Sulfadiazine, sulfisoxazole can reach CSF if used in large dose and can be used in treatment of meningitis.
- Metabolism: mainly in liver by acetylation → inactive.
- Excretion: mainly by kidney and there is part excreted unchanged.

4. **Side effects:**

1. GIT: anorexia, nausea, vomiting.
2. Headache, mental depression.
3. Cyanosis due to methaemoglobinemia.
4. Allergic reactions with cross reaction with other sulfa drugs:

   ▶skin rash, dermatitis, fever, erythema multiform of Stevens Johnson syndrome (serious, may fatal skin and mucus membrane eruption).

5. Blood dyscrasis: agranulocytosis, acute haemolytic anemia, aplastic anemia.
6. Crystalluria due to precipitation of acetylated metabolites in urine, can be prevented or ↓by:

- Give large amount of fluid.
- Keeping the urine alkaline.
- Urine analysis / week.
- Use of more soluble preparation as sulfisoxazole.

7. ↑risk of kernicterus in newborn if sulfonamides used near the end of pregnancy due to displacement of bilirubin from its binding protein.

5. **Therapeutic uses:**

1) First (previously untreated) infections of urinary tract.

– Can use sulfisoxazole as usually sensitive organism.

– But if there is resistant organism can use:

- Sulfamethoxazole + trimethoprim (Co-trimoxazole).
- Quinolone.
- Amipicillin.

2) Bacillary dysentery (shigella diarrhea).

►-Due to resistance we use Co-trimoxazole.

3) Meningococcal infection:

– Treatment: now sulfonamides not used due to resistance, but better to use penicillin G, ampicillin, third generation cephalosporins, or chloramphenicol.

– Chemoprophylaxis:

- Can use sulfisoxazole if organism sensitive to it.
- Rifampin is the drug of choice.
- Minocycline, but cause vestibular toxicity.

4) Nocardiosis:

- Sulfisoxazole is the drug of choice in treatment of infections by nocardia.
- Co-trimoxazole is the alternative.

5) Pneumocystis carinii: but better Co-trimoxazole.

6) Toxoplasmosis: The treatment of choice is combination of sulfadiazine + pyrimethamine.

7) Malaria: we use fansidar (sulfadoxine + pyrimethamine).

8) Sulfasalazine is widely used in ulcerative colitis, enteritis, & other inflammatory bowel disease

9) Topical Agents:

- Sulfacetamide ophthalmic solution or ointment: is effective in the treatment of bacterial conjunctivitis and as adjunctive therapy for trachoma.
- Mafenide & silver sulfadiazine: used for prevention of infection of burn wounds but mafenide is more toxic.

# Trimethoprim

1. **Mechanism of action:**

- Acts by inhibition of dihydrofolate reductase enzyme which is the key enzyme in folate metabolism.
- Consider as one of the folate antagonist.
- Bacteriostatic agent.
- Pyrimethamine inhibits dihydrofolate reductase of protozoa than mammalian cells, so use in treatment of protozoal infection.
- The combination of trimethoprim with sulfonamides causes synergistic effect.

2. **Pharmacokinetics:**

- Well absorbed after oral administration.
- Widely distributed to all tissues especially lung, kidney, CSF.

3. **Side effects:**

- Nausea, vomiting, skin rash.
- Manifestations of folate deficiency as megaloblastic anemia, leucopenia can be prevented by use of folinic acid.

4. **Therapeutic use:**

- Trimethoprim can be used alone in treatment of acute urinary tract infection.

# Trimethoprim-sulfamethoxazole (Co-trimoxazole)

- It is an example of combination treatment which leads to synergestic action.

1. **Mechanism of action:**

- Sulfamethoxazole inhibits dihydropteroate synthetase enzyme.

- Trimethoprim inhibits dihydrofolate reductase enzyme.

2. **Advantages of this combination:**

1. Synergistic effect i.e. ↑the activity of both drugs.
2. Wider antibacterial range.
3. This combination is bactericidal rather than bacteriostatic.
4. ↓ development of resistance (but may developed to gram +ve organism as staph aureus).

3. **Ratio of the combination:**

- We use trimethoprim: sulfamethoxazole in ration of 1:5 but trimethoprim has more lipid solubility than sulfamethoxazole, so has more Vd so the concentration in plasma becomes 1:20 which provided optimal synergistic ratio for most microorganisms.

4. **Side effects:**

1. GIT: anorexia, nausea, vomiting, may diarrhea.
2. Headache, mental depression.
3. Hypersensitivity reactions: rash, Stevens Johnson syndrome
4. Blood dyscrasis
5. Folate deficiency: megaloblastic anemia, leucopenia, thrombocytopenia.

5. **Therapeutic uses:**

1. Urinary tract infections by enterobacteriacae, effective in acute, chronic, recurrent infections.
2. Bacterial prostatitis.
3. Shigella diarrhea.
4. Typhoid fever treatment (best drugs: ceftriaxone, fluoroquinolones & other drugs: ampicillin, chloramphenicol).
   - Can be used to eradicate carrier state from gall bladder (other drugs are fluoroquinolones, ampicillin).
5. Treatment of bacterial respiratory tract infections (not in strep pharyngitis as it ineffective in eradication of organism).
6. Treatment of infection by pneumocystis carinii.
7. Nocardiosis.