Unit-2
Pharmacology- III

B.Pharma 6th Sem Notes

Unit: 2

3. Chemotherapy

- General principles of chemotherapy.
- Sulfonamides and cotrimoxazole.
- Antibiotics- Penicillins, cephalosporins, chloramphenicol, macrolides, quinolones and fluoroquinolins, tetracycline and aminoglycosides

General principles of chemotherapy:

Introduction:

- **Definition:**
  Chemotherapy is the use of chemical substances (drugs) to destroy or inhibit the growth of **infective microorganisms** (bacteria, viruses, fungi, parasites) or **cancer cells** without causing significant damage to the host tissues.
- The term was introduced by **Paul Ehrlich (Father of Chemotherapy)** in the early 20th century.
- **Goal:** Selectively target the disease-causing organism or abnormal cells with minimal harm to normal cells.

Principles of Chemotherapy:

- Treatment of infectious diseases by destroying or inhibiting growth of harmful microorganisms while causing minimal harm to normal host cells and tissues.

Classification of Chemotherapy Agents:

A. Antibacterial agents

- **By mechanism:**
  1. **Inhibitors of cell wall synthesis** – Penicillins, Cephalosporins, Vancomycin
  2. **Inhibitors of protein synthesis** – Tetracyclines, Aminoglycosides, Macrolides
  3. **Inhibitors of nucleic acid synthesis** – Fluoroquinolones, Rifampicin, Metronidazole
  4. **Antimetabolites** – Sulfonamides, Trimethoprim
  5. **Cell membrane disruptors** – Polymyxins

B. Antiviral agents

- Anti-HIV: Zidovudine, Nevirapine
- Anti-herpes: Acyclovir
- Anti-influenza: Oseltamivir

C. Antifungal agents

- Polyenes: Amphotericin B, Nystatin
- Azoles: Ketoconazole, Fluconazole
- Echinocandins: Caspofungin

D. Antiprotozoal agents

- Antimalarials: Chloroquine, Artemisinin
- Anti-amoebic: Metronidazole
- Anti-leishmanial: Sodium stibogluconate

E. Antihelminthic agents

- Albendazole, Mebendazole, Ivermectin

F. Anticancer drugs

- Alkylating agents: Cyclophosphamide
- Antimetabolites: Methotrexate, 5-Fluorouracil
- Mitotic inhibitors: Vincristine, Paclitaxel
- Topoisomerase inhibitors: Etoposide

General Mechanisms of Chemotherapy:

Chemotherapeutic Agents

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Target site in microbe/cancer cell

↓

Inhibit essential process (cell wall, protein, DNA synthesis)

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Growth inhibition or cell death

Sulfonamides

Definition:

- Sulfonamides are a class of **synthetic bacteriostatic antibiotics**.
- They were the first effective chemotherapeutic agents to be used systemically for the prevention and cure of bacterial infections in humans.
- They are derivatives of para-aminobenzenesulfonamide (sulfanilamide).

Mechanism of Action:

- The action of sulfonamides is based on **competitive antagonism**. Bacteria need to synthesize their own folic acid to survive, as they cannot use pre-formed folic acid from their environment. An essential precursor in this synthesis is **para-aminobenzoic acid (PABA)**.
- Sulfonamide drugs look very similar to PABA, so they trick the bacteria into using the drug instead. This blocks the bacteria from making the folic acid they need, which stops them from growing and multiplying.
- Human cells are unaffected because they do not synthesize their own folic acid; they obtain it from their diet.

Uses:

The use of sulfonamides alone has decreased due to bacterial resistance and the development of less toxic antibiotics. However, they are still used for:

- **Urinary Tract Infections (UTIs):** Especially when combined with trimethoprim (as cotrimoxazole).
- **Topical Infections:** Silver sulfadiazine is applied topically to prevent and treat infections in burn wounds.
- **Eye Infections:** Sulfacetamide eye drops are used for bacterial conjunctivitis.
- **Nocardiosis:** A serious bacterial infection affecting the lungs, skin, or brain.
- **Toxoplasmosis:** Often in combination with pyrimethamine.

Adverse Effects:

- **Crystalluria:** The drug can precipitate in the urine, forming crystals that can damage the kidneys and cause obstruction. Patients are advised to drink plenty of water.
- **Hypersensitivity Reactions:** Rashes, fever, and photosensitivity are common. Severe, life-threatening reactions like **Stevens-Johnson syndrome (SJS)** can also occur.
- **Hematological Effects:** Can cause hemolytic anemia in patients with a G6PD deficiency, aplastic anemia, or agranulocytosis.
- **Kernicterus:** In newborns, sulfonamides can displace bilirubin from albumin, leading to high levels of free bilirubin in the blood, which can cross the blood-brain barrier and cause brain damage. For this reason, they are contraindicated in pregnant women near term, newborns, and breastfeeding mothers.

Cotrimoxazole

Definition Cotrimoxazole is not a single drug but a **fixed-dose combination** of two antibiotics:

1. **Sulfamethoxazole** (a sulfonamide)
2. **Trimethoprim**

The two drugs are combined in a 5:1 ratio (Sulfamethoxazole:Trimethoprim) to produce a **synergistic and bactericidal** effect.

Mechanism of Action:

- Cotrimoxazole works by causing a **sequential blockade of the folic acid synthesis pathway** in bacteria. This two-step inhibition is highly effective.

1. **Step 1 (Sulfamethoxazole):** As described above, sulfamethoxazole competitively inhibits the enzyme *dihydropteroate synthase*, blocking the conversion of PABA to dihydrofolic acid.
2. **Step 2 (Trimethoprim):** Trimethoprim then blocks the next step in the pathway. It powerfully inhibits the enzyme *dihydrofolate reductase*, which prevents the conversion of dihydrofolic acid to tetrahydrofolic acid (the active form of folic acid).

This sequential blockade is much more effective than either drug alone (synergism) and often results in killing the bacteria (bactericidal action), whereas each agent alone is only bacteriostatic.

Uses Cotrimoxazole has a broader spectrum of activity and is used to treat a variety of infections:

- **Urinary Tract Infections (UTIs):** It's a very common and effective treatment for both uncomplicated and complicated UTIs.
- **Respiratory Infections:** Effective for acute exacerbations of chronic bronchitis and otitis media (middle ear infection), particularly in children.
- **Pneumocystis jirovecii Pneumonia (PJP):** It is the drug of choice for both the treatment and prevention of this severe fungal pneumonia, which is common in immunocompromised individuals (e.g., those with HIV/AIDS).
- **Gastrointestinal Infections:** Used for traveler's diarrhea and shigellosis.
- **Nocardiosis and Toxoplasmosis:** As mentioned for sulfonamides.

Adverse Effects The adverse effects of cotrimoxazole are generally the sum of those caused by its two components:

- **Sulfonamide-related effects:** All the adverse effects listed for sulfonamides (crystalluria, hypersensitivity, SJS, hematological issues) can occur with cotrimoxazole.
- **Trimethoprim-related effects:**
  - **Bone Marrow Suppression:** Trimethoprim can interfere with human dihydrofolate reductase (though its affinity for the bacterial enzyme is thousands of times greater), leading to megaloblastic anemia, leukopenia, or thrombocytopenia, especially in patients with a folate deficiency.
  - **Hyperkalemia:** It can block sodium channels in the kidney's collecting tubules, similar to the diuretic amiloride, leading to potentially dangerous increases in blood potassium levels.
- **Gastrointestinal Issues:** Nausea, vomiting, and loss of appetite are common.

Easy in Table (For easily to understand)

Drug/Class	Mechanism of Action	Uses	Adverse Effects
Sulfonamides	Inhibit dihydropteroate synthase → ↓ folic acid	UTIs, nocardiosis, burns, trachoma, toxoplasmosis	Rash, crystalluria, kernicterus, hemolysis
Cotrimoxazole	Sulfamethoxazole + Trimethoprim → block 2 steps in folate synthesis	UTIs, PCP pneumonia, typhoid, shigellosis, traveller's diarrhoea	Above + megaloblastic anemia, leukopenia

Antibiotics- Penicillins, cephalosporins, chloramphenicol, macrolides, quinolones and fluoroquinolins, tetracycline and aminoglycosides

Antibiotics:-

Definition

- Antibiotics are **chemical substances** produced by microorganisms (or synthesized artificially) that **inhibit the growth** of or **destroy other microorganisms** in low concentrations.
- They can be **bactericidal** (kill bacteria) or **bacteriostatic** (inhibit growth).

Classification of Antibiotics

A. Based on mechanism of action:

1. **Inhibition of cell wall synthesis**
    - **β-lactams:** Penicillins, Cephalosporins
    - Vancomycin
2. **Inhibition of protein synthesis**
    - **50S inhibitors:** Chloramphenicol, Macrolides (Erythromycin, Azithromycin), Clindamycin
    - **30S inhibitors:** Tetracyclines, Aminoglycosides
3. **Inhibition of nucleic acid synthesis**
    - Quinolones & Fluoroquinolones (Ciprofloxacin, Levofloxacin) – inhibit DNA gyrase
    - Rifampicin – inhibits RNA polymerase
4. **Antimetabolites**
    - Sulfonamides, Trimethoprim – inhibit folic acid synthesis
5. **Disruption of cell membrane function**
    - Polymyxins

A. Penicillins

Mechanism of Action:

- Inhibit **transpeptidase enzyme** → block cross-linking of peptidoglycan in bacterial cell wall → cell lysis (**bactericidal**).
- Active mainly against **gram-positive** organisms.

Uses:

- Streptococcal infections, pneumococcal pneumonia
- Syphilis (Penicillin G)
- Rheumatic fever prophylaxis
- Gonorrhoea (Penicillin G benzathine for susceptible strains)

Adverse Effects:

- Hypersensitivity reactions (rash → anaphylaxis)
- Diarrhoea
- Neurotoxicity (high doses)
- Superinfection

B. Cephalosporins

Mechanism of Action:

- β-lactam antibiotics, same as penicillin – inhibit cell wall synthesis.
- Classified into **5 generations** (higher generations → more gram-negative coverage).

Uses:

- Respiratory tract infections, urinary tract infections
- Septicemia, meningitis (3rd gen: Ceftriaxone)
- Gonorrhoea (Ceftriaxone)
- Skin and soft tissue infections

Adverse Effects:

- Hypersensitivity (cross-reactivity with penicillins)
- Diarrhoea
- Nephrotoxicity (rare)
- Superinfection

C. Chloramphenicol

Mechanism of Action:

- Binds to **50S ribosomal subunit** → inhibits **peptidyl transferase** → blocks protein synthesis (**bacteriostatic**).

Uses:

- Typhoid fever (alternative to fluoroquinolones)
- Meningitis (when penicillin allergy present)
- Rickettsial infections

Adverse Effects:

- **Aplastic anemia** (rare but fatal)
- **Gray baby syndrome** (in neonates – immature liver metabolism)
- GI upset

D. Macrolides (Erythromycin, Azithromycin, Clarithromycin)

Mechanism of Action:

- Bind **50S ribosomal subunit** → inhibit translocation → block protein synthesis (**bacteriostatic**).

Uses:

- Respiratory infections (pneumonia, pertussis)
- Chlamydial infections
- Alternative to penicillin in allergy

Adverse Effects:

- GI upset (motilin receptor stimulation)
- Hepatotoxicity (cholestatic hepatitis)
- QT interval prolongation

E. Quinolones & Fluoroquinolones

Mechanism of Action:

- Inhibit **DNA gyrase** (topoisomerase II) and topoisomerase IV → prevent DNA replication (**bactericidal**).

Uses:

- Urinary tract infections
- Typhoid fever (Ciprofloxacin, Ofloxacin)
- Respiratory infections
- Gastroenteritis

Adverse Effects:

- GI upset
- Tendonitis, tendon rupture
- CNS effects (dizziness, headache)
- Contraindicated in children & pregnancy (cartilage damage)

F. Tetracyclines (Tetracycline, Doxycycline)

Mechanism of Action:

- Bind **30S ribosomal subunit** → block attachment of aminoacyl-tRNA → inhibit protein synthesis (**bacteriostatic**).

Uses:

- Rickettsial infections
- Chlamydia

- Acne
- Cholera
- Malaria prophylaxis (Doxycycline)

Adverse Effects:

- GI upset
- Teeth discoloration, bone growth retardation (children)
- Photosensitivity
- Hepatotoxicity

G. Aminoglycosides (Gentamicin, Amikacin, Streptomycin)

Mechanism of Action:

- Bind **30S ribosomal subunit** → cause misreading of mRNA & inhibit initiation complex → abnormal proteins (**bactericidal**).

Uses:

- Severe gram-negative infections
- Tuberculosis (Streptomycin)
- Synergistic with β-lactams for some infections

Adverse Effects:

- **Nephrotoxicity**
- **Ototoxicity** (hearing loss, vestibular damage)
- Neuromuscular blockade (rare)