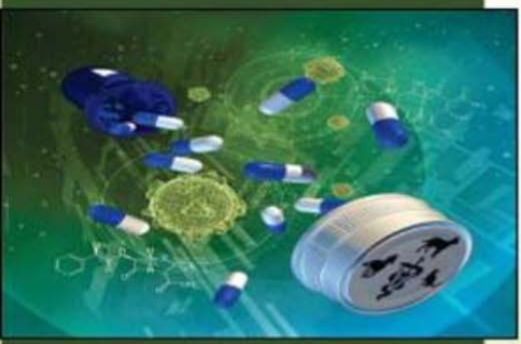
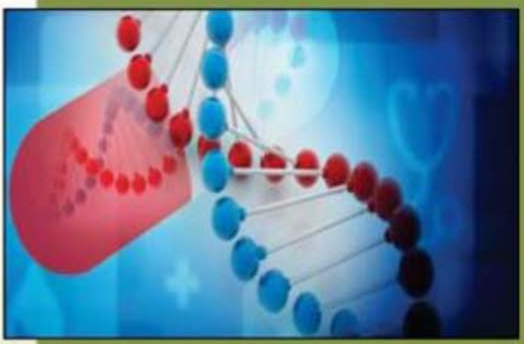
AS PER PCI REGULATIONS

THIRD YEAR B. PHARM.
SEMESTER-VI

# PHARMACOLOGY-III

Dr. S. B. BHISE  Mrs. M. S. BHISE





NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

# A Text Book of

# PHARMACOLOGY - III

**As Per PCI Regulations**

## THIRD YEAR B. PHARM.

**Semester - VI**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# Preface

This is the third book in the series of books related to Pharmacology. The book has been written as per the syllabus prescribed by PCI. Earlier two titles viz Pharmacology I and Pharmacology II have been published by Nirali Prakashan.

The topics like monoclonal antibodies, biosimilars have never appeared in the earlier text books. Relevant preparations of these new types of drugs have been updated in the book. In the coming years, these new drugs are going to occupy higher market share. Hence, the students should be aware about their details. Efforts have been made to include strength and trade names of most of the drugs, as available in Indian market. Still, newer trade names will be updated as and when they appear in Indian market.

Mechanisms of actions, therapeutic uses, adverse reactions, drug interactions and pharmacokinetic details of most of the drugs have been included. This information is likely to be updated from time to time.

A special feature of the book is in the form of appendices. First appendix gives full form of commonly used abbreviations in the book. Second appendix gives explanation of clinically used difficult terms. This appendix is of special importance to students in getting clarity. At the end, generic names of all the drugs referred in the text have been arranged alphabetically and their trade names have been indicated in bold. This is in addition to list of preparations under every category of drugs.

Most of the drugs are mentioned as trade names by clinical practitioners and pharmaceutical company. Trade names are of special importance in case of combination drugs. In addition, summary of every chapter is provided at the end. The summary includes names of drugs and their classification. The summary will students to recollect every chapter in a nutshell, especially useful at the time of revision and examination.

It is expected that the book will be welcomed by teachers and students of pharmacy. Still, if there is any constructive criticism including deficiencies, the authors will welcome feedback from all stakeholders. We hope that the book will be a good addition as a text book of Pharmacology.

**Dr. S. B. Bhise**
**Mrs. M. S. Bhise**

## Acknowledgement

We are extremely thankful to Mrs. Roshan Shaikh for technical editing of the content of the book. Encouragement from Prof. S. B. Gokhale and support from Mr. Jignesh Furia is kindly acknowledged. We are also thankful to Mr. Sameer Tuli for his able assistance.

Nirali Prakashan and their employees are acknowledged for their active support in bringing out the book at an appropriate time.

**Dr. S. B. Bhise**
**Mrs. M. S. Bhise**

# Syllabus

**UNIT - I** **[10 Hours]**

1. **Pharmacology of Drugs Acting on Respiratory System**
   (a) Anti-asthmatic drugs.
   (b) Drugs used in the management of COPD.
   (c) Expectorants and anti-tussives.
   (d) Nasal decongestants.
   (e) Respiratory stimulants.
2. **Pharmacology of Drugs Acting on the Gastrointestinal Tract**
   (a) Antiulcer agents.
   (b) Drugs for constipation and diarrhoea.
   (c) Appetite stimulants and suppressants.
   (d) Digestants and carminitives.
   (e) Emetics and anti-emetics.

**UNIT - II** **[10 Hours]**

3. **Chemotherapy**
   (a) General principles of chemotherapy.
   (b) Sulphonamides and cotrimoxazole.
   (c) Antibiotics - Penicillins, Cephalosporins, Chloramphenicol, Macrolides, Quinolones and Fluoroquinolins, Tetracyclines and Aminoglycosides.

**UNIT - III** **[10 Hours]**

4. **Chemotherapy**
   (a) Anti-tubercular agents.
   (b) Anti-leprotic agents.
   (c) Anti-fungal agents.
   (d) Anti-viral drugs.
   (e) Anthelmintics.
   (f) Antimalarial drugs.
   (g) Antiamoebic agents.

**UNIT - IV** **[08 Hours]**

5. **Chemotherapy**
   (a) Urinary tract infections and sexually transmitted diseases.
   (b) Chemotherapy of malignancy.
6. **Immunopharmacology**
   (a) Immuno-stimulants.
   (b) Immunosuppressants.
   (c) Protein drugs, Monoclonal antibodies, target drugs to antigen.
   (d) Biosimilars.

**UNIT - V** **[07 Hours]**

**7. Principles of Toxicology**

(a) Definition and basic knowledge of acute, sub-acute and chronic toxicity.

(b) Definition and basic knowledge of genotoxicity, carcinogenicity, teratogenecity and mutagenicity.

(c) General principles of treatment of poisoning.

(d) Clinical symptoms and management of barbiturates, morphine, organophosphorous compounds and lead, mercury and arsenic poisoning.

**8. Chronopharmacology**

(a) Definition of rhythm and cycles.

(b) Biological clock and their significance leading to chemotherapy.

# Contents

*Unit* ... **1**

# PHARMACOLOGY OF DRUGS ACTING ON RESPIRATORY AND GASTROINTESTINAL SYSTEMS

Upon completion of this section, the student should be able to

- Understand pharmacological details (classification, mechanism of action, therapeutic effects, clinical uses, adverse reactions, contraindications and drug interactions) of following drugs
  - Drugs acting on asthma
  - Drugs acting on COPD
  - Expectorants and antitussives
  - Nasal decongestants
  - Respiratory stimulants
  - Drugs acting on peptic ulcer
  - Drugs for constipation
  - Drugs for diarrhea
  - Drugs on respiratory system
  - Appetite stimulants and suppressants
  - Digestant and carminative drugs
  - Emetic and antiemetic drugs

## (A) DRUGS ACTING ON RESPIRATORY SYSTEM

### 1.1 ANTI-ASTHMATIC DRUGS

The term asthma means "to stay awake in order to breathe". It is a chronic inflammatory disease in which the patient suffers from reversible episodes of airways obstruction due to bronchial hyper-responsiveness. The symptoms of asthma are breathelessness, wheezing, cough and chest tightness with worsening of these symptoms at night. It can be classified as either extrinsic or intrinsic. If it is associated with specific allergen like pollen grain, then it is called as extrinsic. Unlike this, when there is no identifiable external factor, then it is called as intrinsic asthma. Extrinsic asthma is episodic while intrinsic asthma is perennial.

**Pathophysiology of Asthma:**

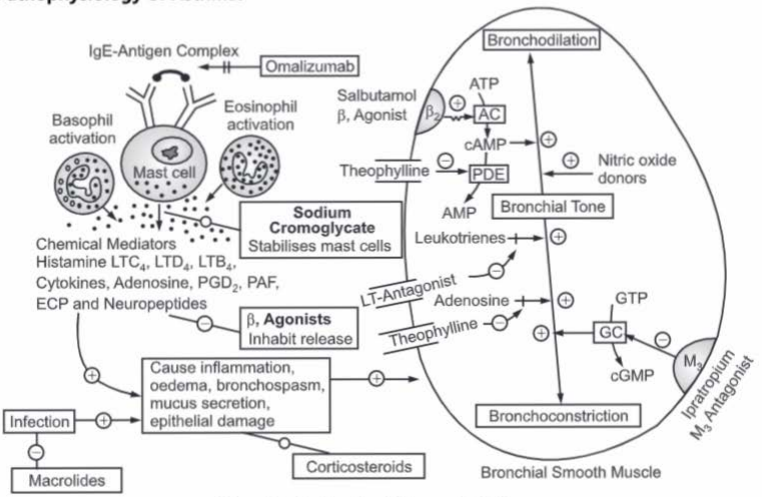



**Fig. 1.1: Pathophysiology of Asthma**

Pathophysiology of asthma is depicted in Fig. 1.1. Antigens like pollen grains sensitize individuals by promoting the production of IgE type of antibodies which remain circulating in the blood or are attached to the mast cells of nasal/bronchial tissues and basophils. On subsequent exposure to the same antigen, there is a antigen-antibody reaction on the surface of lung mast cells causing release of mediators like histamine, serotonin, $PGD_2$ and leukotrienes like $LTC_4/LTD_4$. Both leukotrienes are powerful broncho-constrictors.

In the delayed phase, mast cells release leukotrienes like $LTB_4$ and cytokines like IL-4, IL-5 and IL-13. Eosinophils, basophils and alveolar macrophages are rich in these mediators. There are few other mediators like adenosine, neurokinin-A and platelet activating factor (PAF) which together cause inflammation, increased vascular permeability, chemotaxis of neutrophils and eosinophils, broncho-constriction and bronchial hypersensitivity.

**Classification of Anti-asthmatic Drugs:**

There are six classes of anti-asthmatic drugs. Details of these classes, along with sub-classification, wherever applicable along with relevant examples are mentioned below:

- Bronchodilators
  - Selective β2 agonists like Salbutamol
  - Non-selective sympathomimetics like Ephedrine
  - Anti-cholinergics like Ipratrotium
  - Methylxanthines like Theophylline

- Corticosteroids
  - Orally active corticosteroids like Prednisolone
  - Parenteral corticosteroids like Hydrocortisone
  - Inhalational corticosteroids like Beclomethasone
- Mast cell stabilisers like
  - Sodium cromoglycate
- Leukotriene modulators
  - 5-Lipoxygenase inhibitor like Zileuton
  - Cysteinyl leukotriene-antagonist like Zafirlukarst
- Monoclonal anti-IgE antibody like
  - Omalizumab
- Miscellaneous like
  - Nitric oxide donors

**(a) Bronchodilators:**

They relieve asthmatic symptoms and improve pulmonary functions by relaxing the bronchial smooth muscle. They provide symptomatic relief and may not control the disease process. They are categorised into four groups as follows: Selective $\beta_2$-agonists, Non-selective sympathomimetics, anti-cholinergic and methylxanthine.

**(i) Selective $\beta_2$-agonists:** They activate $\beta_2$-adrenoceptors present on airway smooth muscle and enhance the release of cAMP by activating adenylyl cyclase enzyme. See Fig. 1.1. The mast cells have $\beta_2$-adrenergic receptors which also respond to them.

They exert the effect by following mechanisms:

- Relaxing airway smooth muscle.
- Inhibiting release of broncho-constricting chemical mediators from mast cells.
- Inhibiting microvascular leakage, and
- Increasing the mucociliary transport through the effect on ciliary activity.

The examples of drugs in this category are: Salbutamol (Albuterol), Terbutaline, Remiterol, Fenoterol, Salmeterol, Formoterol, Bambuterol and Pirbuterol. They can be further sub-classified as short acting and long acting. Terbutaline, Salbutamol, Remiterol, Fenoterol and Pirbuterol are short acting; while Salmeterol, Bambuterol and Formoterol are long acting highly lipid soluble drugs. Their half life is around 12 hours.

Among short acting $\beta_2$-agonists, Terbutaline and Salbutamol are most commonly used. they can be either administered orally or by inhalation. They can also be given by intramuscular or intravenous route. When inhaled, these drugs produce effective broncho-dilatation with minimal cardiac stimulation. Inhaled drugs are the drugs of choice for managing acute broncho-spasm. Terbutaline can be safely used even during pregnancy.

Salmeterol, Bambuterol and Formoterol are highly lipid soluble with a longer half life. Salmeterol can function as a slow-release depot. These drugs are useful for treating nocturnal asthma or for long- term prevention of asthma attacks.

When given by inhalation, the adverse effects are minimal. Oral administration can cause muscle tremors and tachycardia. Continued use of these drugs can result in diminished responsiveness. Concurrent use of glucocorticoids or methylxanthines can provide long-term benefit; however the patients should be watched for hypokalaemia. When they are used as inhalations, fluorocarbon propellants are used as carriers. They may sensitize the myocardium to toxic effects of catecholamines.

**Preparations:**

- Salbutamol: 2 mg, 4 mg tab, 100 µg metered dose inhaler (MDI): **Asthalin;** 2 mg/5 ml syrup, 4 mg, 8 mg controlled release tablets, 100 µg (MDI): **Ventrolin;** 100 µg/puff (MDI): **Derihaler**
- Terbutaline: 2.5 mg, 5 mg tab, 1.5 mg/5 ml syrup, 250 µg/puff MDI: **Bricanyl**
- Bambuterol: 10 mg, 20 mg tab: **Betaday;** 10 mg, 20 mg tab, 1 mg/ml syrup: **Bambudil, Roburol**
- Salmeterol: 25 mg/puff MDI: **Salmeter, Serobid**
- Formoterol : 12 µg/puff MDI: **Foratec**

**(ii) Non-selective sympathomimetics :** The drugs in this category include Epinephrine (adrenaline), Ephedrine, Isoproterenol and Orciprenaline (metaproterenol). Amongst these drugs, Epinephrine activates both α and β receptors; while Isoproterenol and Orciprenaline activate β receptors without differentiating between $\beta_1$ and $\beta_2$ receptors. Due to non-selectivity, these drugs may cause cardiac stimulation along with broncho-dilatation. Epinephrine is rarely used due to availability of selective $\beta_2$ stimulants. Metaproterenol is a longer acting derivative of Isoproterenol with more prominent $\beta_2$ action. It can be given orally or by inhalation. However selective $\beta_2$ agonists are preferred.

**Preparations:**

- Mephentermine: 10 mg tab, 15 mg/ml injection: **Mephentine**

**(iii) Anticholinergic:** The muscarinic receptor antagonists used for the treatment of asthma include aerosol preparations of Ipratropium, Oxitropium and Tiotropium. They are less effective than $\beta_2$ agonists. They cause broncho-dilatation by binding to $M_3$ receptors located on airway smooth muscle. They prevent the action of acetyl choline released from parasympathetic nerves. They act by reducing the levels of c GMP as a consequence of blocking $M_3$ receptors. See figure 1.1. These drugs do not differentiate between $M_2$ and $M_3$ receptors. $M_2$ receptors are located on pre-synaptic sites; hence their blockade reduces secretion of acetylcholine. This limits effectiveness of anti-cholinergics. Being quaternary compounds, they are poorly absorbed and cause less systemic adverse reactions. They decrease mucus secretions but have less drying effect on mucus. They do not cross blood-brain-barrier (BBB); hence they do not cause adverse reactions related to CNS. Tiotropium is longer acting as compared to Ipratropium. A combination of Ipratropium with a $\beta_2$ agonist like Salbutamol has synergistic action in controlling asthma.

**Preparations:**

- Ipratropium: 0.5 mg/2.5 ml solution;Inhaler/nebuliser: **Atrovent, Apovent, Ipraxa, Rinatec**
- Oxitropium: 200 µg twice/thrice a day: **Oxivent**
- Tiotropium: Inhalation powder 18 µg cap: **Spiriva handhaler**

**(iv) Methylxanthine:** The drugs in this category include Theophylline, Aminophylline, Diprophylline and Choline theophyllinate. Their effects as anti-asthmatics are mediated through following mechanisms:

- Inhibition of the enzyme phosphodiesterase III, located in airway smooth muscle and phosphodiesterase IV located in eosinophils and mast cells. Both the isoenzymes are responsible for the metabolism of c AMP. Elevated levels of c AMP, due to inhibition of phosphodiesterase isozymes lead to broncho-dilatation.
- Blockade of adenosine receptors located on airway muscles ($A_1$) and those located on mast cells ($A_3$). See Fig. 1.1.

Theophylline exhibits bronchodilatory, anti-inflammatory and immunomodulatory effects. It is primarily used in the management of asthma and to treat COPD. Theophylline also relieves dyspnoea associated with pulmonary oedema which develops from CHF. These drugs are usually used in combination with $\beta_2$ agonists.

Theophylline has some limitations. It has a narrow therapeutic window (10-20 µg/ml). Above 20 µg/ml, it causes CNS stimulation leading to nausea and vomiting. Above 40 µg/ml, it causes tremors followed by seizures, agitation, diuresis, arrhythmias and fever. It has several drug interactions. Enzyme inducers like Phenytoin, Carbamazepine, Phenobarbitone and Rifampicin decrease levels of Theophylline. Smoking reduces levels of Theophylline due to enzyme induction. Drugs like alcohol, Zileuton, Cimetidine, Erythromycin and Ciprofloxacin increase the plasma levels and prolong the half-life of Theophylline due to enzyme inhibition.

**Preparations:**

- Theophylline: 80 mg/15 ml Elixir: **Broncordil;** 400 mg, 600 mg tab: **Od-phyllin;** 400 mg, 600 mg slow release tab: **Theoday;** (Etofylline 84.7 mg/ml + Theophylline 25.3 mg/ml) injection: **Theoder, Deriphyllin**
- Doxofylline: 400 mg tab: **Doxobid, Doxfree;** 400 mg tab, 100 mg/5 ml syrup: **Bestofyline**
- Aminophylline: 100 mg tab, 25 mg/ml injection: **Minophyl, Aminophylline**
- Acebrophylline: 100 mg cap: **AB-phylline, Bestophylline-A, Unobro**

**(b) Corticosteroids:**

Following actions of corticosteroids help in reversing the pathologic process of bronchial asthma:

- They enhance $\beta_2$-adrenoceptor response by up-regulating the $\beta_2$ receptors in lung cells and leukocytes

- They inhibit the release of prostaglandins and leukotrienes ($LTC_4$, $LTD_4$ and $LTE_4$) and thus prevent smooth muscle contraction, vascular permeability and airway mucus secretion
- They produce eosinopenia, which prevents cytotoxic effects of the mediators released from eosinophils, and
- They inhibit formation and release of cytokines and chemical mediators from mast cells and eosinophils. This leads to prevent recruitment, proliferation and activation of leukocytes.

Thus corticosteroids are not prophylactic but are effective in preventing late asthmatic responses and in decreasing bronchial hyper-responsiveness.

Corticosteroids are used in three formulations as follows:

**(i) Aerosol corticosteroids:** The drugs in this category are: Beclomethasone, Triamcinolone, Fluticasone, Budesonide and Flunisolide. They are least absorbed into systemic circulation; hence they produce minimal systemic adverse reactions. Hence they are more suitable along with $\beta_2$-agonist aerosol for long term treatment of asthma. In therapeutic doses, adverse reactions like dryness of mouth, voice changes and oral candidiasis are less severe.

Ciclesonide has a better topical: systemic activity ratio. After inhalation, it is degraded by esterase enzymes present in bronchial epithelium to release active form of Ciclesonide which provides local effect. Even if it is absorbed, it gets bound to plasma proteins; hence it minimises its exposure to glucocorticoid receptors in skin, eye, bone etc. As a result it has minimum risk of systemic toxicity.

**(ii) Oral corticosteroids:** Commonly used drugs in this category are: Prednisone, Prednisolone and Methylprenisolone. Prednisone is a prodrug and is converted to Prednisolone in liver. These drugs have a shorter half-life in comparison to Betamethasone or Dexamethasone. These drugs are preferred for a period of 7-10 days during which adrenocoytical suppression and related systemic toxicity are lowered.

**(iii) Parenteral corticosteroids:** They are used only in severe acute asthma with appropriate dosages depending on clinical need. The drugs used in this category are: Hydrocortisone and Methylprednisolone.

**Preparations:**

- Betamethasone: 1 mg, 0.5 mg tab: **Betnelan;** 1 mg, 0.5 mg tab, 0.5 mg/ml drops, 4 mg/ml injection: **Betnesol, Solubet**
- Deflazacort: 6 mg tab: **Asteride;** 1 mg, 6 mg tab: **Cortisure;** 1 mg, 6 mg, 30 mg tab: **Defnalon, Defza**
- Dexamethasone: 0.5 mg tab, 4 mg/ml injection: **Dexona, Wymesone;** 0.5 mg tab: **Dexasone, Demisone**
- Hydrocortisone: 25 mg/5 ml injection: **Wycort,** 100 mg/vial injection: **Efcorlin**
- Methylprednisolone: 4 mg, 8 mg, 16 mg tab: **Nicort, Zempred;** 1 mg, 40 mg, 125 mg, 500 mg/vial injection: **Succimed**

- Prednisolone: 4 mg, 16 mg, 40 mg, 125 mg, 500 mg/vial injection: **Melpred;** 5 mg/ml syrup: **Predone;** 5 mg, 10 mg, 20 mg tab: **Wysolone**
- Triamcinolone: 4 mg tab, 10 mg/ml, 40 mg/ml injection: **Kenacort, Tricort;** 4 mg tab: **Ledercort**

**Topical and inhalational steroids:**

- Beclomethasone: 0.25% cream: **Zovate, Beclate;** 50 µg, 100 µg, 200 µg, 250 µg/puff Metered Dose Inhaler (MDI): **Beclate**
- Betamethasone: 0.05% cream: **Betamil, Lupiderm;** 0.1% cream and scalp lotion: **Betnovate**
- Clobetasol: 0.05% ointment/cream: **Lobate, Cloderm, Clop**
- Dexamethasone: 0.1% cream: **Millicortenol**
- Fluocinolone: 0.025% ointment/cream: **Lusi, Flucocin**
- Fluticasone: 0.05% ointment/cream: **Flutivate;** 0.05% cream, 0.005% ointment, 0.05% lotion: **Zoflut;** 50 µg, 125 µg/puff MDI: **Floease;** 50 µg/puff MDI: **Flomist, Flutiflo**
- Halcinonide: 0.1% ointment: **Cortilate**
- Hydrocortisone: 0.5% cream; **Hycort;** 0.1% cream: **Locidlipo cream**
- Mometasone: 0.1% ointment/cream, 0.1% solution: **Topcort, Cutizone**
- Triamcinolone: 0.1% ointment: **Ledercort**
- Budesonide: 100 µg, 200 µg/puff MDI: **Budecort, Neohaler, Budez**
- Ciclesonide: 200 µg Rotacap inhaler: **Ciclohale**

**(c) Mast Cell Stabilisers:**

The drugs in this categoty are: Sodium chromoglycate (Cromolyn sodium) and Nedocromil sodium. Both drugs are chemically related and belong to a chemical group called as chromones. They are non-broncho-dilating, non-steroidal drugs used for prophylaxis of asthma. Both are available as metered-dose aerosol. Chromolyn sodium powder can be inhaled through a nebuliser. Both drugs prevent degranulation and subsequent release of chemical mediators from mast cells. They stabilise mast cells by preventing trans-membrane influx of $Ca^{++}$ ions provoked by antigen-IgE antibody reaction on the membrane of mast cells. In addition, they also inhibit leukocyte activation and chemotaxis. The stabilising effects on mast cells appear to be specific for lung-cell because they inhibit mast cell degranulation in human lung but not in skin.

When taken regularly (2-3 puffs, 3-4 times daily), for prophylaxis, both agents reduce the need for broncho-dilator ($\beta_2$-agonist) or anti-inflammatory (corticosteroid) treatment in terms of reduction in the dose as well as frequency. Both drugs are highly ionised and have least systemic absorption on inhalation. They are well tolerated, making them especially useful in children. There are minor adverse reactions like throat irritation, dryness of mouth, wheezing or mild headache. these drugs are reserved for prophylactic use in the management of chronic and seasonal asthma and are ineffective in the treatment of acute attacks including status asthmaticus.

**Preparation:**

- Sodium chromoglycate: 1 mg metered dose aerosol; 2% eye drops: **Fintal**

**(d) Leukotriene Modulators:**

The drugs in this category are: Zileuto (enzyme inhibitor) and Zafirlukast, Montelukast, Pranlukast, Iralukast. They act as receptor blockers.

Leukotrienes are powerful mediators of inflammation, cause recruitment of leukocytes, stimulate broncho-constriction and increase capillary permeability leading to pulmonary oedema. In addition, they also stimulate mucus secretion and decrease muco-ciliary clearance. They are generated from arachidonic acid via 5-lipooxygenase pathway. There are three types of leukotrienes: $LTC_4$, $LTD_4$ and $LTE_4$. They activate leukotriene receptors leading to broncho-constriction. The effects of leukotrienes can be prevented either by inhibiting the leukotriene synthesis or by blocking their stimulatory effect on the receptors. The synthesis of leukotrienes can be blocked by inhibiting the 5-lipooxygenase enzyme by the drug Zileuton. All drugs in this category are used as adjuvants with inhaled corticosteroids in poorly responding patients. They reduce the dosage of $\beta_2$ adrenergic agonists as well as inhaled corticosteroids for the purpose of maintenance.

Zileuton is given orally at 6 hourly intervals and is well absorbed from GIT. Due to hepatotoxicity, it has been withdrawn from some countries. Liver disease is the absolute contraindication for this drug. It inhibits metabolism of Theophylline and Warfarin and hence their dosage should be reduced, when used along with Zileuton.

Zafirlukast is rapidly absorbed after oral administration, but its bioavailability decreases when given along with food. Hence it is administered 2 hours before meals, at 12 hourly intervals. It has a half-life of 10 hours. It is metabolised by liver by the enzyme CYP2C9 and hence can inhibit the metabolism of Warfarin. Adverse effects include GIT distress and headache.

Montelukast has the advantage of being administered once daily. In addition, its bioavailability is not affected by food. It can be safely used in children above 5 years of age. Iralukast is similar to Montelukast. Pranlukast is a newer addition. All drugs are given orally.

In rare cases, treatment of patients with leukotriene receptor antagonists is associated with Churg-Straus syndrome causing vasculitis, eosinophilia and worsening of asthma.

**Preparations:**

- Montelukast: 4 mg, 5 mg, 10 mg tab: **Monti, Romilast, Montelast**
- Zafirlukast : 10 mg, 20 mg tab: **Zuvair**

**(e) Monoclonal Anti-IgE Antibody:**

The only drug in this category is Omalizumab. It is a monoclonal antibody.

The drug is targeted against IgE, so that IgE cannot bind to its receptors present on mast cells and basophils. The drug has following characteristics:

- It inhibits binding of IgE to mast cells and basophils
- It inhibits the activation of IgE already bound to mast cells and thus prevent their degranulation, and
- It down-regulates the receptor named FcE R-1, present on mast cells and basophils.

Omalizumab neutralises free IgE in circulation by forming a high affinity IgE-Omalizumab complex. Thus it is an antibody which is antagonist to IgE antibody. The drug is indicated for asthmatic patients who are not adequately controlled by inhaled corticosteroids and who demonstrate sensitivity to aero-allergens. It is not suitable for status asthmaticus.

**(f) Miscellaneous Drugs:**

The drugs in this category are nitric oxide donors. It is known that inhalation of nitric oxide is useful in treating bronchial asthma because it dilates pulmonary blood vessels and relaxes airway smooth muscles. In upper airways, it is considered to be a non-noradrenergic non-cholinergic (NANC) neurotransmitter.

**Status Asthmaticus:**

It is a potentially life-threatening acute attack of severe asthma needing immediate treatment. Most often hospitalisation is necessary. The treatment includes a high concentration (40-60%) of oxygen with high flow rate along with high doses of inhaled short –acting $\beta_2$ agonists. In addition, high doses of systemic corticosteroids like 30-60 mg of Prednisolone by mouth and 200 ml of Hydrocortisone intravenously should be given. If necessary, 0.5 mg of Ipratropium through inhalation may be added.

## 1.2 DRUGS USED IN THE MANAGEMENT OF COPD

The word COPD indicates Chronic Obstructive Pulmonary Disease.

**Pathophysiology of COPD:**

COPD is a disease state characterised by the progressive obstruction of air flow. It differs from asthma. Unlike asthma, the obstruction of air flow, indicated by an abnormal decline in the Forced Expiratory Volume in one second ($FEV_1$) is more or less progressive and largely irreversible. COPD is commonly associated with cigarette smoking, respiratory infections, environmental pollution and occupational exposures, e.g. in persons working in cement or cotton industries. COPD is usually associated with chronic bronchitis and in later stages of emphysema.

In chronic bronchitis, there is enlargement of mucous glands, increase in mucus production and thickening of bronchial wall. Emphysema is characterised by enlargement of air spaces, destruction of lung parenchyma, loss of lung elasticity and closure of small airways.

The inflammatory component of COPD, leading to airway pathology makes it distinct from asthma. COPD patients show increased neutrophil activation as opposed to eosinophil and mast cell activity. In COPD, macrophage activation releases chemotactic factors like $LTB_4$ and IL-8 from neutrophils. In addition, proteases are also released which destroy lung parenchyma.

**Treatment of COPD:**

The treatment of COPD has following objectives:

- To reduce air flow obstruction.
- To reduce respiratory symptoms and improve quality of life, and
- To prevent and treat secondary complications like hypoxaemia, infections and *cor pulmonale* (right sided heart failure).

Following are the options for the treatment of COPD:

- The most important therapeutic intervention is to stop smoking.
- Influenza vaccine may be given to patients of COPD every year and a proper antibiotic therapy should be provided if patient develops purulent sputum.
- The first line of drug therapy is use of broncho-dilators. Short acting $\beta_2$ agonists should be tried initially. Since airway muscle tone is controlled by parasympathetic system, use of anti-muscarinic drugs like Ipratropium, Oxitropium or Tiotropium is beneficial.
- A xanthine like Theophylline may also be administered orally. It improves respiratory muscle function. In addition, due to ionotropic effects, it is additionally useful in *cor pulmonale*. Persistent nocturnal symptoms like cough or wheezing are helped by night-time use of long acting Theophylline.
- Some patients of COPD, receiving broncho-dilator therapy, exhibit better response to oral corticosteroids (eg Prednisolone 30-40 mg per day for 15 days). If better responses are achieved, then inhalational corticosteroids should be given. During this time, dose of oral glucocorticosteroids is gradually tapered.
- In patients of severe COPD and persistent hypoxaemia, use of domicilary oxygen therapy for 15 hours a day reduces mortality and risk of complications like cor pulmonale and neuro-psychological impairment.

For preparations of $\beta_2$ agonists, Xanthines and inhalational corticosteroids see respective parts under section 1.1.

## 1.3 EXPECTORANTS AND ANTITUSSIVES

**Expectorants**

These drugs either increase the volume or decrease the viscosity (or both) of the respiratory secretions and facilitate their removal by ciliary action and coughing. They act by two mechanisms: mucokinetic or mucolytic.

**(a) Mucokinetic Expectorants:**

These expectorants stimulate the flow of respiratory tract secretions by stimulating the bronchial secretory cells to increase the volume and stimulate the ciliary movement to facilitate removal of secretions. They also have a reflex irritant effect on gastric mucosa, which initiates the reflex secretions of respiratory tract fluid. Commonly used mucokinetic expectorants are: volatile oils, ammonium chloride, sodium citrate, guaiacol and guaifenesin.

Essential oils like anise oil, eucalyptus oil provide mild expectoration by stimulating the bronchial secretory cells. Ammonium chloride is a gastric irritant which reflexly enhances bronchial secretions. However in large doses it can produce metabolic acidosis. Sodium citrate is yet another conventional expectorant. After absorption, citrate gets converted to bicarbonate in vivo and mucus becomes less viscous in alkaline pH. Guaiacol and guaifenesin are safe expectorants with proven efficacy. Guaifenesin is less irritating derivative of guaiacol. After absorption, guaifenesin is secreted through bronchial glands to increase airway secretions and mucosal ciliary activity. It is administered orally in a dose of 100-200 mg BD or TDS.

**Preparations:**

- Guaifenesin, ammonium chloride, sodium citrate (combined formulations): (Dextromethorphan 5 mg + Chlorpheneramine 2.5 mg + Guaifenesin 50 mg + Ammonium chloride 60 mg) /5 ml syrup: **Grilinctus**
- (Diphenhydramine 14 mg + Ammonium chloride 138 mg + Sodium citrate 57 mg + Menthol 1.1. mg)/ 5 ml syrup: **Benadryl**
- (Diphenhydramine 8 mg + Ammonium chloride 100 mg + Guaifenesin 50 mg + Bromhexine 4 mg + Menthol 1 mg)/5 ml syrup: **Zeet Expectorant**

**(b) Mucolytic Expectorants:**

Mucolytics decrease the viscosity of mucus secretions and facilitate its removal by ciliary action or coughing. Commonly used mucolytics are: Acetylcysteine, Carbocysteine, Bromhexine, Ambroxol and Dornase-alpha.

**Acetylcysteine** is a mucolytic which decreases viscosity of mucus by splitting the disulphide (−S−S−) bonds of mucoproteins. This action is facilitated by alkaline pH in the range of 7-9. It is administered by nebulisation (3-5 ml of 20% solution) through a face mask in patients of cystic fibrosis and chronic bronchitis. Mechanical suction of liquefied secretions may be necessary because it produces large amounts of secretions which need to be removed. Adverse effects include nausea, vomiting, stomatitis and broncho-spasm. The drug is also used to treat paracetamol toxicity.

**Carbocysteine** is related to Acetylcysteine. It has a protected sulfyhydryl (−SH) group and cannot work through splitting disulphide bond of mucus. It is given orally in a dose of 250-500 mg TDS. Adverse effects are similar to that of Acetylcysteine.

**Bromhexine** depolymerises mucopolysaccharides of mucus and also increase lysosomal enzyme activity which breaks fibre-network of the sputum. Usual oral dose is 8-16 mg TDS. Adverse effects include GIT upset and rhinorrhoea.

**Ambroxol** is a metabolite of Bromhexine and has similar mode of action. It is more useful if mucus plugs are present. Usual oral dose is 30 mg BD or TDS.

**Dornase- alpha** is a highly purified solution of recombinant human DNase, an enzyme which selectively cleaves DNA. Purulent pulmonary secretions in cystic fibrosis contain very high amounts of extracellular DNA which is released by degeneration of neutrophils in response to infection. The drug in a dose of 2.5 mg once daily hydrolyses accumulated DNA in the sputum of patients of cystic fibrosis and reduces the viscosity of sputum.

**Preparations:**

- Acetylcysteine: 600 mg tab, 200 mg/ml injection (can be taken by nebulisation): **Mucomix**.
- Carbocysteine: 375 mg cap, 250 mg/5 ml syrup: **Mucodyne;** (Amoxycillin 500 mg + Carbocysteine 150 mg) cap; (Amoxycillin 250 mg + Carbocysteine 150 mg) cap: **Carbomox**.
- Bromhexine: 8 mg tab, 4 mg/5 ml syrup: **Bromhexine**.
- Ambroxol : 30 mg tab, 30 mg/5 ml liquid, 7.5 mg/ml drops: **Ambrolite, Mucolite**

**Antitussives:**

Antitussives suppress the frequency as well as the intensity of coughing without affecting the normal elimination of excessive secretions from the respiratory tract. They are classified into four sub-categories as follows:

**(a) Centrally Acting Antitussives:**

Drugs under this category include opioid derivatives like Codeine, Pholcodeine, Noscapine and non-opioid derivatives like Dextromethorphan, Noscapine and Pipazethate. All these drugs exert antitussives action on CNS and suppress cough centre which mediates the cough reflex.

**Codeine** is a semi-synthetic opioid analgesic with potent cough suppressant action. It is administered orally in the dose of 10 mg BD or TDS. At this dose it exhibits lesser addiction liability and lesser constipation. Over-dose can result in respiratory depression, convulsions, postural hypotension and tachycardia.

**Pholcodeine** is structurally related to Codeine but is slightly more potent, longer acting and better tolerated than Codeine. It causes lesser constipation and drowsiness than Codeine and is more suited for long term use. It is given orally in a dose of 10-15 mg BD.

**Dextromethorphan** is the methylester of dextroisomer of Levorphanol. It has least addiction liability, no analgesic action, less constipating effects and minimal drowsiness. As antitussives, it is less potent than Codeine. It is given orally in the dose of 10 mg TDS. It is the most commonly used cough suppressant and is used in combination with other agents like anti-histamines and broncho-dilators in cough mixtures.

**Noscapine** is a naturally occurring opium alkaloid. It has no analgesic activity, drowsiness and addiction liability. It has minimal constipating effects and is a popular cough suppressant. It is given orally in a dose of 15 mg TDS. High doses produce nausea, headache and tremors.

**Pipazethate** is a phenothiazine group of synthetic antitussives, occasionally used in cough mixtures. It has negligible CNS depressant effects. It is also given orally in a dose of 40 mg TDS.

Morphine itself is a powerful cough suppressant, but it is normally not preferred because of addiction potential. It is reserved only for cough in terminal illness.

**Preparation:**

- Codeine (phosphate): 15 mg/5 ml: **Codeine linctus**

**(b) Central as well as Peripherally Acting Antitussives:**

There is only one drug in this category. **Benzonatate** is an antitussives structurally related to the local anaesthetic Tetracaine. It not only inhibits the afferent cough impulses to suppress the central cough centre, but also inhibits the pulmonary stretch receptors. Thus it has both central as well as peripheral mode of action. It exerts mild local anaesthetic action also. It is administered orally in a dose of 100-200 mg TDS. Adverse reactions include drowsiness, nausea, headache and in high doses, vertigo.

**(c) Peripherally Acting Antitussives:**

**Prenoxdiazine** acts by inhibiting pulmonary stretch receptors to relieve broncho-spasm. It has a moderate antitussives action. It is administered orally in a dose of 100-200 mg TDS.

**(d) Miscellaneous Drugs**

**Demulcents** can also be listed as indirect peripherally acting cough suppressants. They provide a protective coating over sensory receptors on pharynx. These include honey, liquorice, syrup tolu and syrup vasaka.

**Local anaesthetics** like Lidocaine and Bupivacaine can be applied on pharynx and larynx to reduce the sensitivity of sensory receptors for cough in this area. They are usually used to treat the cough associated with bronchoscopy and can also be used for patients who are refractory to other cough therapy.

Antitussives, in general, should not be used for treating cough associated with asthma, chronic bronchitis or bronchiectasis, because they can cause harmful retention and thickening of sputum.

**Preparations:**

- Prenoxdiazine: 100 mg, 200 mg tab: **Prenoxid**
- Lidocaine (Lignocaine): 2% jelly, 2% viscous, 2% and 4% solution, 10% and 15% spray: **Gesicaine, Xylocaine**

## 1.4 NASAL DECONGESTANTS

The drugs in this category are: Naphazoline, Oxymetazoline and Xylometazoline. In addition, Pseudoephedrine, which is a stereoisomer of Ephedrine and Phenylpropanolamine are sympathomimetic non-catecholamine drugs are also used as nasal decongestants.

Naphazolin, Oxymetazoline and Xylometazoline are used in rhinorrhoea and to check epistaxis. These drugs are predominantly $\alpha_1$ agonists. Oxymetazoline has some $\alpha_2$ agonistic action also causing hypotension.

Pseudoephedrine and Phenylpropanolamine are used in common cold oral formulations for the relief in nasal congestion. Phenylpropanolamine, due to risk of haemorrhagic stroke in young women and hypertensive has been withdrawn from the market.

**Preparations:**

- Naphazoline: 0.1% nasal drops: **Privine, Fenox**
- Oxymetazoline: 0.05% nasal drops: **Xynose;** 0.5% nasal drops: **Synarest**
- Xylometazoline: 0.1% nasal drops: **Otrivin**
- Pseudoephedrine : (pseudoephedrine 30 mg + Chlorpheneramine 2 mg + Bromhexine 4 mg)/5 ml: **Cheston Expectorant**

## 1.5 RESPIRATORY STIMULANTS

Drugs in this category mainly act on brain stem and spinal cord to stimulate respiratory and vasomotor centres. In higher doses they produce convulsions.

The only drug in this category is **Doxapram.** It acts by exciting central neurons. At low doses it is more selective for the respiratory centre. It is a short acting drug with higher margin of safety. It increases tidal volume and rate of respiration. It is used for following effects:

- To counteract post- anaesthetic respiratory depression
- As an aid to COPD. It is useful in hypoxaemic (reduced oxygen in blood) and hypercapnic (increased carbon dioxide in blood) respiratory failure where it is used along with oxygen inhalation, and
- To abolish episodes of apnoea in premature infants not responding to Theophylline. In such cases it is given by slow intravenous infusion at the rate of 2-5 mg/ min upto a maximum dose of 4 mg/Kg

It is contraindicated in the cases of hypoxaemic normocapnic respiratory failure, asthma and in respiratory failure due to neurological and muscular disease as well as epilepsy. Adverse effects include restlessness, tachycardia and in higher doses convulsions and cardiac arrhythmia.

**Preparations:**

- Doxapram: 4 mg/ml injection: **Caropram**

# (B) PHARMACOLOGY OF DRUGS ACTING ON THE GASTROINTESTINAL TRACT

## 1.6 DRUGS ACTING ON PEPTIC ULCER

A localised loss of gastric or duodenal mucosa leads to formation of peptic ulcer, which includes gastric as well as duodenal ulcer.

### (I) Physiology of Gastric Secretion

The events leading to acid secretion are depicted in Fig. 1.2. Gastric acid is secreted by the parietal cells in gastric mucosa. The basolateral membrane of these cells contains receptors for following three stimulants. See Fig. 1.2.

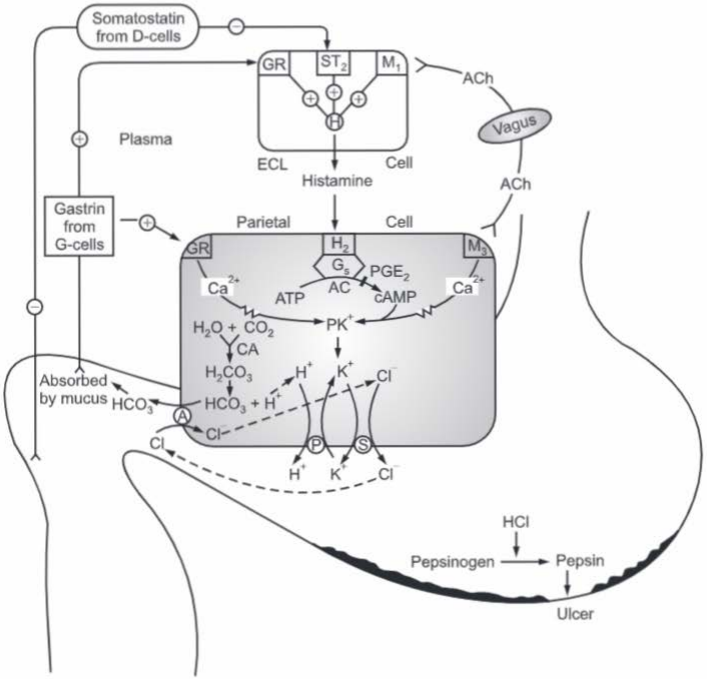



**Fig. 1.2: Mechanism of gastric acid secretion**

- Gastrin from antral G-cells.
- Histamine from enterochromaffin-like cells (ECL cells).
- Acetyl choline (Ach) from endings of vagus nerve.

The main stimulant for acid secretion is Acetyl choline (Ach) released at the nerve ending of vagus nerve. ACh acts on two types of receptors: $M_1$ and $M_3$. $M_1$ receptors are located on ECL cells and are major source for histamine release. $M_3$ receptors are located on parietal cells and can cause secretion of hydrochloric acid through release of calcium. Gastrin released from G-cell can also stimulate histamine release from ECL cells. Thus, ECL cells are major source for histamine release needed for acid secretion. The peptic cells, found primarily in fundus, synthesise and secrete pepsinogen. The acidic pH < 2.0 cleaves pepsinogen to active pepsin. Too much of pepsin activity erodes gastric mucosa, to form peptic ulcer.

The gastric defence mechanisms include the presence of prostaglandins ($PGE_2$ and $PGI_2$) in the gastric mucosa, the presence of mucin layer over the gastric epithelial cells and the secretion of $HCO_3^-$ into the mucin layer. $PGE_2$ produced by gastric mucosa, inhibits acid secretion by inhibiting cAMP in parietal cells. In addition, $PGE_2$ enhances mucosal blood flow and stimulates secretion of mucus and bicarbonate. The events are shown in figure 1.2.

**(II) Drug Treatment of Peptic Ulcer**

Drugs acting on peptic ulcer are classified in five sub-classes as follows:

**(a) Drugs Which Neutralise Gastric Acid (Antacids):**

**Antacids** are the drugs which neutralise hydrochloric acid in the stomach. Earlier, antacids were the primary treatment for peptic ulcer, gastroesophageal reflux and dyspepsia. Now, $H_2$ receptor antagonists and proton pump inhibitors are used as better alternatives. Antacids are weak bases, which neutralise gastric acid and raise the pH of stomach contents. They decrease the acid load delivered to duodenum and also reduce the activity of pepsin. They may also promote mucosal defence through stimulation of prostaglandin production and partly by forming a protective layer over gastric mucosa. They are normally given between meals and at bed time when symptoms of hyperacidity usually occur. The presence of food in stomach can prolong the neutralising capacity of antacids. Factors like formulation, duration of action and gastric emptying decide benefits from antacids. Liquid formulations are more effective than chewable tablets. Insoluble non-systemic antacids have relatively longer duration of action. Fatty foods delay gastric emptying time.

This group is sub-classified into systemic and non-systemic antacids.

- **Systemic antacids:** e.g. Sodium bicarbonate.

Sodium bicarbonate is the only example in this category. It acts rapidly, has a brief duration of action and raises the pH of gastric secretions from < 2 to 7.4. On neutralising gastric HCl, it forms $CO_2$ and NaCl. Formation of $CO_2$ results in gastric distension and belching; which can be dangerous if ulcer is near perforation. Untreated alkali is readily absorbed from the gastro-intestinal lumen and can raise the pH of blood, causing systemic alkalosis. It may also make urine more alkaline. Absorption of NaCl may increase sodium load and may exacerbate fluid retention in patients of hypertension, CHF and renal insufficiency. A sudden rise in gastric pH (upto 7.4) and release of $CO_2$ promotes release of gastrin, which can cause rebound acidity. Given in sufficient quantity for longer time they can heal duodenal ulcers but are less effective for gastric ulcers.

As indicated above they should not be prescribed for long term use and they should not be given to patients of hypertension, CHF and renal failure.

- **Non-systemic antacids:**

They are poorly absorbed from GIT and do not disturb systemic acid-base balance. They do not elevate urinary pH. They are sub-divided into following three groups:

1. **Buffer type:** e.g. Aluminium hydroxide

The examples in this category are Aluminium hydroxide, Magnesium trisilicate and Magaldrate. They have slow onset but longer duration of action and raise gastric pH only up to 3.5 to 4. Since the pepsin activity is inhibited only around pH 4, these drugs do not cause rebound acidity.

Both Aluminium hydroxide and Magnesium trisilicate neutralise gastric HCl leading to formation of Aluminium chloride and Magnesium chloride respectively; which further react with intestinal bicarbonates leading to formation of Aluminium/Magnesium carbonate. As a result, $HCO_3^-$ is not available for systemic absorption. In fact, these antacids are termed as non-systemic primarily because $HCO_3^-$ ions are not available for systemic effects. In addition, NaCl formed in this process gets reabsorbed to compensate the loss of chloride ions during gastric acid neutralisation. Thus, buffered-type non-systemic antacids do not disturb the acid-base balance of the body.

Aluminium hydroxide causes constipation because of following reasons:

- It forms Aluminium phosphate
- $Al^{+++}$ ions exert smooth muscle relaxant action, and
- Aluminium salts exert mucosal astringent action

Since $Al^{+++}$ bind to $PO_4^{---}$ in intestine and prevents its absorption, it may result in hypophosphataemia (lower phosphates in body). Thus Aluminium hydroxide can also be used to treat hyperphosphataemia and phosphates stones.

Magnesium trisilicate also does not disturb acid-base balance. $SiO_2$, formed during neutralisation reaction, forms a gelatinous coating over gastric mucosa and prolongs the antacid effect. However unlike Aluminium hydroxide, both $MgCl_2$ and $MgCO_3$ generated during reaction with Magnesium trisilicate cause diarrhoea as an adverse effect. See Fig. 1.3.

$$Al(OH)_3 \xrightarrow[\text{Stomach}]{HCl} AlCl_3 \xrightarrow[\text{Intestine}]{HCO_3^-/PO_4^{3-}} Al_2(CO_3)_3 + Al(PO_4)_3 + NaCl$$

$$2MgO \cdot 3SiO_2 \cdot nH_2O \xrightarrow[\text{Stomach}]{HCl} MgCl_2 + SiO_2 \xrightarrow[HCO_3]{\text{Intestine}} Mg(CO_3)_2 + NaCl$$

**Fig. 1.3: Reactions of $Al(OH)_3$ and $2MgO \cdot 3SiO_2 \cdot nH_2O$**

Magnesium salts cause osmotic diarrhoea while Aluminium salts cause constipation. Hence these two are commonly administered together in most of the formulations.

Magaldrate is a hydrated complex of Aluminium-Magnesium hydroxide sulphate with the formula: $Al_5Mg_{10}(OH)_{31}(SO_4)_2.nH_2O$. When it reacts with HCl, it rapidly releases Aluminium hydroxide and Magnesium hydroxide. Freshly released Aluminium hydroxide is more reactive. It is an effective buffer- type non-systemic antacid with prompt and sustained neutralising action.

**2. Non-buffer type:** e.g. Magnesium hydroxide

Drugs in this category are **Calcium carbonate and Magnesium hydroxide.** They are powerful antacids with fast onset of action and raise gastric pH above 7.

Like sodium bicarbonate, **Calcium carbonate** may cause belching due to liberation of $CO_2$. Excessive doses of Calcium carbonate if given along with milk can cause hypercalcaemia, renal insufficiency and metabolic alkalosis, collectively called as milk-alkali syndrome. Acid rebound with calcium carbonate is marked because of sudden rise in gastric pH and partly because calcium chloride itself is a stimulant for gastrin release. Calcium carbonate causes constipation due to formation of calcium stearate in intestine as shown in Fig. 1.4.

$$Ca(CO_3)_2 \xrightarrow[\text{Stomach}]{HCl} CaCl_2 \xrightarrow[\text{Intestine}]{HCO_3^-/\text{Stearate}} Ca(CO_3)_2 + \text{Calcium stearate} + NaCl$$

**Fig. 1.4: Metabolism of $CaCO_3$ in GIT**

**Magnesium hydroxide** neutralises HCl promptly and is an effective antacid. It brings gastric pH up to 7. Acid rebound with Magnesium hydroxide is mild and brief as compared to Calcium carbonate. Liberation of Magnesium carbonate causes diarrhoea. Since $CO_2$ is not generated, belching does not occur. It is usually given along with Aluminium hydroxide. See figure 1.5.

$$Mg(OH)_2 \xrightarrow[\text{Stomach}]{HCl} MgCl_2 \xrightarrow[\text{Intestine}]{HCO_3^-} Mg(CO_3)_2 + NaCl$$

**Fig. 1.5: Metabolism of magnesium hydroxide**

**Drug Interactions**

- By forming inert complexes, $Al^{+++}$, $Ca^{++}$ and $Mg^{++}$ group of antacids decrease the absorption and bioavailability of Tetracyclines, when given concurrently.
- Antacids should not be given within two hours of administration of Tetracyclines, Fluoroquinolones, Itraconazole, Digoxin or Iron salts.
- $Al^{+++}$ group of antacids decrease the bioavailability of phosphates, iron salts and Digoxin. Magnesium salts also decrease the absorption of Digoxin.
- By raising gastric pH and ionisation, antacids decrease the absorption of acidic drugs like Barbiturates, Phenytoin and NSAIDs.

**3. Miscellaneous : e.g. Alginates**

There are two drugs in this category: Simethecon and Sodium alginate.

**Simethecone (dimethyl polysiloxane)** is a silicon polymer and has water repellent properties. It acts as an antifoaming agent and reduces gastric flatulence. It aids proper dispersion of antacid in gastric contents, coats ulcer surface, prevents hiccups and reduce flatulence. It is pharmacologically inert and is not absorbed from GIT. It is used in topical skin preparations to prevent bed sores. It is also called as activated dimethicone.

**Sodium alginate (alginic acid)** is a hydrophilic colloidal carbohydrate derivative extracted from sea weeds. It is used along with antacids or with $H_2$ receptor antagonist, like Ranitidine for the management of heart burn and GastroEsophageal Reflux Disease (GERD).

Sodium alginate is a prototype drug. It reacts with gastric acid to form a viscous gel, called as raft, which floats at the top of gastric contents. The raft acts as mechanical barrier to reduce heart burn and the effects of gastric reflux. Sodium alginate may be combined with buffer – type antacids (containing $Al^{+++}$ + $Mg^{++}$ salts).

**Preparations:**

- Dried aluminium hydroxide gel 840 mg, tab, 610 mg/10 ml gel: **Aludrox.**
- (Alum hydroxide 300 mg + Mg-Al-Silicate 25 mg + Mag hydroxide 25 mg + Simethicone 25 mg) chewable tab; (Alum hydroxide 830 mg + Mag hydroxide 185 mg + Simethicone 50 mg + Sod carboxymethylcellulose 100 mg/10 ml) gel: **Digene.**
- Activated dimethicone 40 mg tab: **Dimol.**
- (Dried alum hydroxide gel 250 mg + Mag hydroxide 250 mg + Dimethicone 50 mg)/5 ml syrup: **Gelusil. Mps.**
- (Magaldrate 400 mg + Simethicone 60 mg) tab/syrup: **Nicid.Mps.**
- (Alginic acid 100 gm + Mag hydroxide 400 mg + Alum hydroxide 200 mg + Simethicone 50 mg) tab: **Visco.**
- (Sodium alginate 200 mg + Alum hydroxide 300 mg + Mag trisilicate 125 mg)/10 ml suspension: **Raftace.**

**(b) Drugs Which Reduce Gastric Acid Secretion:**

Drugs in this category reduce secretion of HCl from stomach. They are further sub-divided into four sub-classes as follows:

**(i) $H_2$-receptor antagonists:** e.g. Ranitidine.

These are most commonly prescribed drugs.

**Mechanism of Action:**

These drugs competitively inhibit $H_2$ receptors on the parietal cells and suppress basal and food-stimulated acid secretion. By blocking the $H_2$ receptors of gastric parietal cells, they block the action of histamine released from enterochromaffin-like cells through gastrin or vagal stimulation. They also inhibit direct stimulation of parietal cells by gastrin or ACh. They markedly reduce gastric acid secretion for a longer duration and also decrease pepsin production but for a shorter period.

They block more than 90% of nocturnal acid but only about 60-70% of day-time food-stimulated acid secretion. Recommended doses maintain at least 50% inhibition up to 10 hours. Hence these drugs are usually given twice daily.

The drugs in this category are Cimetidine, Ranitidine, Famotidine, Nizatidine, Roxatidine and Loxatidine. Cimetidine is relatively less used because of several drug interactions.

Clinical comparison between some of these drugs is presented in Table 1.1.

**Table 1.1: Clinical comparison of $H_2$ blockers**

| Features | Cimetidine | Ranitidine | Famotidine | Roxatidine | Nizatidine |
|---|---|---|---|---|---|
| Relative potency | 1 | 5 | 30 | 8 | 5 |
| Bioavailability (%) | 80 | 50 | 50 | >90 | >90 |
| Cytochrome P-450 inhibition | ++++ | + | 0 | 0 | 0 |
| Endocrinal effects | ++++ | 0 | 0 | 0 | 0 |

**Clinical Uses**

Following are clinical uses of $H_2$ receptor antagonists:

- Gastroesophageal Reflux Disease (GERD)
- Duodenal and gastric ulcer
- NSAIDs-induced ulcers
- Prevention of stress-related gastric bleeding
- Prevention of ulcer recurrence
- Zollinger-Ellison syndrome (ZES)
- Chronic urticaria (increase efficacy of $H_1$ blockers)

Dosages of different $H_2$ blockers are indicated in Table 1.2.

**Table 1.2: Dosages for different $H_2$ blockers**

| Indication | Cimetidine | Ranitidine | Famotidine | Roxatidine | Nizatidine |
|---|---|---|---|---|---|
| 50% acid inhibition | 400-800 | 150 | 20 | 75 | 150 |
| Duodenal/gastric ulcer | 800 HS<br>400 BD | 300 HS<br>150 BD | 40 HS<br>20 BD | 150 HS<br>75 BD | 300 HS<br>150 BD |
| GERD | 800 BD | 150 BD | 20 BD | 75 BD | 150 BD |
| NSAIDs-ulcers | 400 BD | 150 BD | 20 BD | 75 BD | 150 BD |
| Stress related GIT bleeding in ZES | 50 mg/hour infusion | 6.25 mg/hour infusion or 50 mg IV every 6-8 hours | 1.7 mg/hour infusion or 20 mg IV every 12 hours | 75 mg slow IV every 12 hours | Not available |
| Prevention of recurrence | 400 HS | 150 HS | 20 HS | 75 HS | 150 HS |

*: All doses are in mg

Loxatidine is a new addition in this category.

**Adverse Effects:**

Following are the adverse effects related to $H_2$ blockers:

- Headache, fatigue, myalgia and constipation (rare).
- Only Cimetidine may cause mental changes.
- Endocrinal effects observed only with Cimetidine. It inhibits metabolism of estradiol and increases serum prolactin levels leading to gynaecomastia in males and galactorrhoea in females. The effects are observed with long term use only.
- All $H_2$ blockers reduce secretion of intrinsic factor but there is no deficiency of vitamin $B_{12}$, even after prolonged use.
- All $H_2$ blockers cross placental barrier but have no harmful effects on foetus.
- They are secreted in breast milk. It is advised to avoid them during pregnancy and lactation.

**Drug Interactions:**

Following interactions are observed with $H_2$ blockers:

- Antacids reduce absorption of all $H_2$ blockers. A gap of two hours should be kept between administration of antacids and $H_2$ blockers.
- Cimetidine is a potent inhibitor of CYP1A2, CYP2C9, CYP2D6 and CYP3A4. Hence plasma half life of Warfarin, Theophylline, Phenytoin, Quinidine, Tricyclic antidepressants, Benzodiazepines, $Ca^{++}$ channel blockers, oral hypoglycaemic agents, Metronidazole, Alcohol and β-blockers may be prolonged. Negligible interactions occur with other $H_2$ blockers.

**Preparations:**

- Cimetidine: 200 mg tab: **Lock-2;** 200 mg, 400mg tab: **Tymidine, Ulciban**
- Ranitidine: 150 mg, 350 mg tab, 25 mg/ml injection: **Histac, R-loc, Ranitin, Rantac, Zinetac**
- Famotidine: 20 mg, 40 mg tab: **Famocid, Famtac, Topcid**
- Roxatidine: 75 mg, 150 mg SR tab: **Rotane, Zorpex**

**(ii) Proton Pump Inhibitors (PPIs): eg Omeprazole**

PPIs are the most widely used drugs for peptic ulcer and related disorders. The drugs in this category are Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole and Rabeprazole. Except for Pantoprazole, which can also be given intravenously, all are given orally. Since these drugs are acid labile and can be destroyed by gastric acid, they are available in enteric coated formulations.

**Mechanism of Action:**

All PPIs are pro-drugs and are converted to active forms within gastric parietal cells. During their passage through intestine, their enteric coating dissolves and the pro-drug is absorbed from the intestine. Being weak bases, they are lipid soluble in alkaline medium and get absorbed by passive absorption across lipid membranes. Once they reach the parietal

cells, they are exposed to acidic environment where they get rapidly ionised and get concentrated. In parietal cells, they undergo a molecular rearrangement to an active "sulfenamide cation". PPIs-Sulfenamide is an active form and makes a disulfide bond with –SH group of the proton pump, thereby inactivating it irreversibly and reducing acid secretion. PPIs also inhibit gastric mucosal carbonic anhydrase and reduce $HCO_3^-$ secretion in mucus.

**Pharmacokinetics:**

Their comparative bioavailability and dosages for every indication are shown in Table 1.3.

**Table 1.3: Clinical comparison of PPIs**

| Features | Omeprazole | Esomeprazole | Lansoprazole | Pantoprazole | Rabeprazole |
|---|---|---|---|---|---|
| Bioavailability (%) | 55 | 70 | 85 | 77 | 52 |
| Doses for the indications | | | | | |
| Duodenal and gastric ulcer | 20 OD<br>40 OD | 20 OD<br>20 OD | 15 OD<br>30 OD | 40 OD<br>40 OD | 20 OD<br>20 OD |
| GERD | 20 OD | 20 OD | 30 OD | 40 OD | 20 OD |
| NSAID ulcers | 20 OD | 20 OD | 30 OD | 40 OD | 20 OD |
| ZES | 60-120 daily | 60-120 daily | 60-120 daily | 40-240 daily | 60-120 daily |
| *H. pylori* eradication | 20 OD or BD | 40 OD or BD | 30 OD or BD | 40 BD | 20 BD |
| Prevention of recurrences | 20 OD | 20 OD | 15 OD | 40 OD | 20 OD |

All dosages are in mg.

**Clinical Uses:**

Following are the clinical uses of PPIs:

- Treatment of duodenal and gastric ulcer.
- Gastroesophageal Reflux Disease (GERD).
- NSAIDs induced ulcers.
- Prevention of ulcer recurrence.
- Zollinger- Ellison Syndrome (ZES).
- *H. pylori*-associated ulcers: PPIs promote eradication of *H pylori* by raising intra-gastric pH which helps in lowering the MIC of antibiotics used against *H pylori.*

**Adverse Effects:**

Following are adverse effects with PPIs:

- Diarrhoea, headache and abdominal pain (rare).
- They should be used cautiously during pregnancy and lactation.

- They inhibit absorption of vitamin $B_{12}$ on prolonged use.
- They decrease $Ca^{++}$ absorption and may aggravate osteoporosis.
- PPIs produce hypochlorhydria; which can increase the risk of enteric infections like Salmonella and Shigella.
- In patients of *H. pylori*-associated peptic ulcers, long term use of PPIs may increase the risk of chronic inflammation of gastric body.

**Drug Interactions:**

Following are clinically important drug interactions with PPIs:

- A decrease in gastric acidity due to PPIs may decrease absorption of ketoconazole and Digoxin.
- Omeprazole, Esomeprazole and Lansoprazole inhibit CYP2C19 and CYP3A4. Hence they may enhance effects of Warfarin, Phenytoin, Carbamazepine and benzodiazepines by decreasing their metabolism.
- Lansoprazole is a weak enzyme inducer and may enhance elimination of Theophylline.
- Rabeprazole and Pantoprazole exhibit no significant interaction.

**Preparations:**

- Esomeprazole: 20 mg, 40 mg tab: **Es-OD, Esoz, Izra;** (Esomeprazole 20 mg + Domperidon SR 30 mg) cap: **Izra-D, Esoz-D**
- Lansoprazole: 15 mg, 30 mg cap: **Liza, Lanpro, Lancid, Lansofast;** (Lansoprazole 30 mg + Domperidon 10 mg) cap: **Liza-D, Locid-D**
- Omeprazole: 10 mg, 20 mg, 40 mg cap: **Ocid, Lomac, Omez, Protoloc;** (Omeprazole 20 mg + Domperidon 10 mg) cap: **Ocid-D, Domstal-O**
- Pantoprazole: 20 mg, 40 mg tab: **Lupipan, Pantocid, Pantop;** (Pantoprazole 20 mg + Domperidon 10 mg) tab: **Pantop-D, Pan-D**
- Rabeprazole : 10 mg, 20 mg tab: **Repcia, Prorab, R-cid, R-ppi, Rabeloc;** (Rabeprazole (EC) 20 mg + Domperidon (SR) 30 mg) cap: **Rabeloc-RD, Domrab, Esogard**

**(iii) Anti-cholinergics: e.g. Propantheline**

Due to use of $H_2$ receptor antagonists and PPIs, anti-cholinergics are relatively less used. From amongst anti-cholinergics, drugs like Propantheline and Oxyphenonium were preferred because they do not cross blood brain barrier and have lesser side effects. These drugs exhibit adverse effects like blurred vision, dry mouth, constipation and urinary retention. They block acid secretion during fasting more effectively than that stimulated by food. In addition, by increasing gastric emptying time, they prolong exposure of ulcer to gastric acid. This makes them unsuitable for treatment of ulcer. They may exacerbate GERD by allowing reflux of acid-mixed food into the oesophagus.

Some selective $M_1$ receptor blockers of ACh, like Pyrenzepine and Telenzepine are being used for treatment of peptic ulcer. These drugs heal as well as prevent the recurrence of duodenal ulcers. They are not available in India.

**(iv) Prostaglandin analogues: e.g. Misoprostol**

Prostaglandins play an important role in gastric defence mechanisms against peptic ulcer. $PGE_2$ produced by gastric mucosa inhibits acid secretion by inhibiting cAMP and gastrin release. In addition, $PGE_2$ enhances mucosal blood flow and stimulates the secretion of mucus and bicarbonates. A stable methyl analogue of $PGE_1$ is available as Misoprostol. It is given in a dose of 200 µg orally, four times a day. It is approved for healing of peptic ulcer in patients using NSAIDs and in chronic heavy smokers. However its plasma half life is only 25-30 minutes and needs frequent dosing.

The commonest side effects with Misoprostol are diarrhoea and colicky pain. Other GIT effects include nausea, vomiting and flatulence. Headache and dizziness can occur in some patients. It should not be given to patients who are either pregnant or may become pregnant; because it may cause uterine contractions.

**Preparations:**

- Misoprostol: 200 µg tab: **Mesopil, Misolast, Misolup**

**(c) Mucosal protective drugs: e.g. Sucralfate.**

**(i) Sucralfate:**

The first drug in this category is Sucralfate. It is an ammonium salt of sulphated sucrose. In acidic environment, at pH < 4, it polymerises by cross-linking of molecules and forms a sticky gel over ulcer which acts as acid-resistant physical barrier.Dietary as well as mucosal proteins get adsorbed over this coat forming another layer to provide further resistance. It also stimulates mucosal $PGE_2$ synthesis and $HCO_3^-$ secretion. It also binds to epithelial and fibroblast growth factors which promotes mucosal repair. It promotes ulcer healing, although it has no acid neutralising capacity. It delays gastric emptying. It is not effective in preventing or healing NSAIDs-induced ulcers. It is administered in a dosage of 1 gm four times daily, because it adheres to ulcer for about 6 hours. Since it is not absorbed, it causes no systemic adverse effects. However it binds phosphate ions in intestine. Hence it may cause hypophosphataemia. Antacids should not be given with Sucralfate, because its polymerisatrion occurs only in acidic condition. Sucralfate adsorbs drugs like tetracyclines, fluroquinolones, $H_2$ blockers, Phenytoin and Digoxin resulting in decreased absorption of these drugs.

It is used as a glycerine paste for treating stomatitis. Its gel is used for burn dressing and bed sores. In higher doses, it may be used to prevent phosphate stones in kidney. It is also available in combination with local anaesthetics.

**Preparations:**

- Sucralfate: 1 gm/10 ml syrup: **Sparacid, Sucracid;** 1 gm tab: **Sucrase, Recolfate;** (Sucralfate 1 gm + Oxetacaine 20 mg/10 ml) syrup: **Sucromark;** 1 gm/5 ml gel: **Pepsigard;** (Sucralfate 7% wt/wt + Metronidazole 1% wt/wt + Lignocaine 4% wt/wt) cream for burn dressing: **Sucral-ANO**

**(ii) Colloidal Bismuth Subcitrate and Bismuth subsalicylate**

This is the second drug in the category of mucosal protective drugs. In gastric acidic media, colloidal bismuth subcitrate forms an acid-resistant protective coating over ulcer base. It stimulates $PGE_2$, mucus and bicarbonate secretion. It dislodges *H pylori* from the surface of gastric mucosa and has direct antimicrobial activity against ulcer causative organism. It is administered in a dosage of 120 mg orally four times a day. It heals peptic ulcer within 4-8 weeks. Many ulcers which do not heal after $H_2$ blocker treatment respond well to colloidal bismuth. It causes blackening of stool and darkening of tongue. Prolonged use may cause bismuth toxicity leading to osteodystrophy and encephalopathy. Antacids should not be taken with colloidal bismuth because they decrease its efficacy. Ranitidine bismuth citrate is also available, which on hydrolysis by gastric acid releases bismuth and Ranitidine.

**Preparations:**

- Colloidal bismuth subcitrate: 120 mg tab: **Trimo, Denol.**

**(d) Ulcer healing drugs: e.g. Carbenoxolone.**

Use of Carbenoxolone has become outdated because of adverse effects like hypertension, sodium and water retention, hypokalaemia. Better drugs are available.

**(e) Anti-*Helicobacter pylori* drugs: e.g. Amoxycillin.**

About 90% cases of duodenal ulcers, 60-70% cases of gastric ulcers and 50% cases of non-ulcer dyspepsia harbour *H pylori*. This organism is able to survive in acidic environment by its ability to produce urease, which hydrolyses urea to ammonia. Ammonia neutralises gastric HCl to create a neutral protective cloud around the bacteria. In addition, *H pylori*, by disturbing normal feedback mechanism, cause more secretion of gastric acid through release of more gastrin in response to food. *H pylori* also produces various proteolytic enzymes like proteases and lipases which further decrease mucosal barrier and damage epithelial cell membrane causing chronic inflammation of gastric mucosa finally leading to ulcer.

PPIs are more effective in eradicating *H pylori*. PPIs also exhibit anti-microbial activity against *H pylori* in vitro and lower MIC of antibiotics against *H pylori*. All PPIs, except Pantoprazole, have been approved in combination of antibiotics for eradication of *H pylori*.

The combination therapy for 14 days is better. Triple therapy has good success in containing *H pylori*. In case if the organism is resistant to triple therapy, quadruple therapy is advised.

**Preparations:**

- (Lansoprazole 30 mg + Clarithromycin 250 mg + Tinidazole 500 mg): **Heligo combipack**
- (Omeprazole 20 mg + Amoxycillin 750 mg + Tinidazole 500 mg): **Helibact-combipack**
- (2 caps of Lansoprazole 30 mg + 2 tabs of Tinidazole 500 mg + 2 tabs of Clarithromycin 250 mg**): Pylokit**

- (2 tabs of Pantoprazole 40 mg + 2 tabs of Amoxyllcillin 750 mg + 2 tabs of Tinidazole 500 mg): **Zovanta kit**

## 1.7 DRUGS FOR CONSTIPATION

Constipation means delayed passage of faeces through the intestine with defaecation process remaining normal. Evacuation is often associated with straining and is usually incomplete.

Majority of cases suffer with only functional constipation, which can be corrected by one of the following ways:

(a) An increase in roughage, ie fibrous content in daily diet.
(b) An increase in daily fluid intake.
(c) An increase in physical activity.
(d) Not neglecting nature's call.
(e) Adjusting the daily routine.
(f) Selecting alternative drug which cause constipation as a side effect. Drugs like Morphine, Anticholinergics, Aluminium/Calcium group of antacids cause constipation.
(g) Correcting the underlying pathology; eg: Vitamin B1 deficiency, hypothyroidism, diabetes mellitus and Parkinson's disease.

If all these non-therapeutic measures fail, then laxatives or purgatives can be used. Laxatives result in elimination of soft semi-solid stool while purgatives provide more watery evacuation. Laxatives and purgatives are further sub-divided in four and two sub-classes respectively. They are discussed below:

### 1.7.1 Laxatives

Laxatives are used in following conditions:

- To treat constipation.
- To avoid undue straining at defaecation in cases having hernia, haemorrhoids or cardiovascular disease.
- Before or after any anorectal surgery.
- In bed-ridden patients.

Laxatives have mild activity and are usually faecal softeners. Their sub-classes are discussed below:

**(i) Bulk-forming Laxatives:**

The examples in this category include Wheat bran, Psyllium husk, Ispaghula husk, semi-synthetic cellulose like carboxy-methyl-cellulose (CMC) and polycarbophils.

These are luminally active, hydrophilic, indigestible vegetable fibres. They stimulate peristalisis and defaecation reflexes by increasing faecal bulk due to their water absorbing and retaining capacity.

Adequate amount of water must be taken with all bulk-forming laxatives. Laxative effect appears within 1-3 days. Bran powder or husk can also be sprinkled over food.

Since these drugs are not absorbed, there are no systemic adverse effects. however, bacterial digestion of vegetable fibres within the colon may lead to bloating and flatus causing abdominal discomfort.

**Preparations:**

- Ispaghula husk: 100 gm, 300 gm powder: **Naturolax, Eva-Q, Inulax, Fibril, Fibradiat**
- Psyllium muciloid: 100 gm powder: **Isovac**
- Calcium polycarbophil: 625 mg tab: **Fibotab**

**(ii) Osmotic Laxatives:**

The example in this category is Lactulose (10 gm/15 ml).

Lactulose is luminally active, non-absorbable, indigestible disaccharide. It increases faecal bulk by hydrophilic action as well as osmotic action.

It is given in a dose of 10 gm BD or TDS with plenty of water to produce 2-3 soft stools per day. Latency period is 1-3 days.

It is non-toxic and is also suitable for long term use. Flatulence is common, cramps may occur in few patients. Some patients may have nausea due to its peculiar sweet taste.

In addition to constipation, Lactulose is also used for treatment of hepatic encephalopathy. Lactulose is degraded to lactic acid and converts ammonia (generated in hepatic encephalopathy) to ionised $NH_4^+$ salt which is then excreted.

**Preparations:**

- Lactulose 10 gm/15 ml solution: Evict, Laxan, Looz, Mtlac, Swilac

**(iii) Lubricant Laxatives:**

The example in this category is Liquid paraffin.

It is luminally active drug. It is pharmacologically inert oil. It is a faecal lubricant and stool softener as it retards water absorption from the stool.

It is given in the dosage of 15-30 ml per day at bed time. Latency period is 1-3 days.

It is not palatable but can be given in emulsified form or with juices. Frequent use leads to deficiency of fat soluble vitamins (A, D, E and K) as they are carried away with stool in emulsified form. Forcible administration can lead to aspiration lipid pneumonia. It also delays the healing of enteric fistula. It is useful where straining at defaecation is to be avoided.

**Preparations:**

- Liquid paraffin: (Liquid paraffin 3.75 ml + Milk of magnesia 11.25 ml)/15 ml emulsion/liquid: Cremaffin.

**(iv) Surfactant Laxatives:**

The example in this category is Dioctyl, Sodium sulfosuccinate (Docusate sodium).

It is a luminally active agent which is an anionic surfactant and softens the stool by decreasing the surface tension of fluids in the bowel. It also acts as a wetting agent for the

bowel, because by emulsifying the colonic contents it facilitates mixing of water into fatty substances of the faeces.

It is given orally in the doses of 100-400 mg in divided doses. It is a mild laxative, specially indicated when straining at defaecation is to be avoided. Latency period is 1-3 days.

It is not absorbed and does not cause systemic toxicity. Being bitter in taste, it can cause nausea. Cramps and abdominal pain may occur. Long term use can cause hepatotoxicity. It increases the absorption of liquid paraffin, hence should not be given together.

**Preparations:**

- Docusate sodium: 100 mg tab, 50 mg/5 ml syrup: **Laxicon;** 100 mg capsule: **Cellubril**

## 1.7.2 Purgatives

Purgatives are used for complete cleaning of colon prior to gastro-intestinal endoscopic procedures. They are also needed for post-operative or post-MI bed- ridden patients and to flush out worms after the use of an anthelmintic drug. They are also used to prepare the bowel before surgery or abdominal X-ray and may be needed for neurologically impaired patients. Purgatives either provide semi-fluid stool or lead to watery evacuation. In low doses they can also be used as laxatives. They are sub-divided into two types: osmotic and irritant.

**(i) Osmotic Purgatives:**

One of their types is saline purgative. The examples in this category are Magnesium sulphate, Magnesium hydroxide (milk of magnesia), Sodium sulphate and Sodium phosphate. The second category is of electrolyte osmotic purgative, available as Polyethylene glycol (PEG). Osmotic purgatives lead to watery evacuation.

All osmotic purgatives act on small as well as large intestine. Saline purgatives are soluble inorganic salts which increase the faecal bulk by retaining water due to osmotic effect, which increases peristalisis indirectly. Magnesium salts also release cholecystokinin which further helps in increasing intestinal secretions and peristalisis. PEG is an electrolyte osmotic purgative. It retains water by virtue of its high osmotic nature. It is used in a form of a balanced isotonic solution preparaed by adding sodium chloride, sodium sulphate, sodium bicarbonate and potassium chloride. The isotonic solution of PEG is so designed that no electrolyte shift occurs across the intestinal wall. Therefore the preparation is safe for all patients.

Milk of magnesia, being tasteless, is the most commonly used saline purgative. 30 ml of its 8% w/w suspension is used. Its effects occur within 2-3 hours. PEG-electrolyte osmotic purgative is ingested orally. 4 litres of the solution should be ingested over 2-3 hours for complete colonic cleansing prior to GIT endoscopic procedures. For treatment of chronic constipation, smaller doses of this solution can be used (300-500 ml daily) or 17 gm of the powder in 8 ounces of water per day. The latency period is 2-3 hours.

The saline purgatives should be ingested with enough water, because being irritants, they may induce vomiting. The hyper-osmolar agents may lead to intravascular fluid depletion and electrolyte disturbances. These should never be used on long term basis and should be

avoided in hypertensive as well as CHF patients. Magnesium salts should not be used for prolonged period in patients with renal insufficiency due to risk of hypermagnesaemia. About 20% of ingested magnesium is normally absorbed.

**Preparations**

- Magnesium hydroxide: 8% w/w suspension: **Milk of magnesia**
- Polyethylene glycol (PEG): (PEG 118 gm + Sodium chloride 2.93 gm + Potassium chloride 1.484 gm + Sodium bicarbonate 3.37 gm + Anhydrous sodium sulphate 11.36 gm) sachet or pack: **Peglec, Coloclean**

**(ii) Irritant Purgatives:**

The drugs in this category belong to three sub-classes:

- ❖ Anthraquinone group: eg Senna.
- ❖ Organic irritants: eg Phenolphthalein.
- ❖ Oils: Castor oil.

Irritant purgatives provide soft, semi-fluid stools.

All of them stimulate peristalisis by irritant action on intestinal mucosa. They also stimulate colonic electrolyte and fluid secretion by altering the absorptive and secretory activity of mucosal cells. The examples from Anthroquinone group are Aloe, Senna and Cascara; all occur naturally in the form of plants. Senna is most commonly used. These plant purgatives contain anthraquinone glycosides. On reaching the colon, the bacteria degrade them by separating the active principle called anthrol; which acts either locally or is absorbed into circulation. After being excreted through bile, it stimulates small intestine and causes purgative action.

The second group is of organic irritants which act in the colon. Besides phenolphthalein, Bisacodyl and Sodium picosulfate are other examples in this category. Bisacodyl is metabolised in the intestine into an active deacetylated metabolite. In the colon, sodium picosulfate is converted to an active metabolite which stimulates peristalisis and promotes accumulation of water and electrolytes.

From oils, castor oil is the only example of irritant purgative. Castor oil by itself is non-irritant. It is hydrolysed in intestine by pancreatic lipase to ricinolic acid which increases the intestinal motility.

Senna glycosides (sennoside A and B) are given in a dose of 12-25 mg at bed time. The effect appears within 6 hours. Phenolphthalein is rarely used in a dose of 60-130 mg at bed time. The effect appears within 6-8 hours. Bisacodyl is given in a dose of 5-10 mg at bed time. It is usually effective within 6-8 hours. Castor oil is used in a dose of 15-25 ml in the morning; the effect appears within 3 hours.

Senna glycosides are secreted through milk; hence should be avoided in lactating mothers. They turn urine colour to yellowish brown (acidic urine) or to red (alkaline urine). Chronic use leads to characteristic brown pigmentation of the colon. It is contraindicated in pregnancy to avoid pelvic congestion. All anthraquinones can produce abdominal cramps

and nausea. About 15-20% of phenolphthalein undergoes entero-hepatic circulation and exhibit prolonged action. It turns urine reddish pink in alkaline urine. It may cause skin rash. Its use is very much declined now.

Bisacodyl may cause occasional abdominal cramps and skin rashes. Prolonged use or overdose of sodium picosulfate can cause colonic atony and hypokalaemia. Castor oil is unpalatable, may cause frequent cramping, after-constipation and risk for damaging intestinal mucosa. It is contraindicated in pregnancy to avoid pelvic congestion. Its purgative action is self-limiting.

**Preparations:**

- Bisacodyl: 5 mg tab: **Dulcolax, Julax, Swilax;** 5 mg, 10 mg suppositories: **Dulcolax**
- Sodium picosulfate: 10 mg tab: **Cremalax, Laxicare, Picate**
- Phenolphthalein : (Liquid paraffin 9.54 mg + Phenolphthlein 400 mg + Agar 60 mg)/30 ml emulsion: **Agarol;** (Milk of magnesia 11.25 ml + Liquid paraffin 3.75 ml + Phenolphthlein 50 mg)/15 ml emulsion: **Cremaffin with phenolphthlein**
- Senna alkaloids: Sennoside-B 11.5 mg tab: **Galaxenna;** (Sennoside-A and B 18 mg + Karaya gum 3.1 gm)/5 gm granules: **Evacuol**
- Castor oil: 15-25 ml oil: **Castor oil**

## 1.8 DRUGS FOR DIARRHOEA

Diarrhoea is an abnormal increase in the frequency and the liquidity of stools. Increased motility of GIT and the decreased ability of intestine to absorb water from the stool are the major factors in pathophysiology of diarrhoea. For symptomatic relief of non-specific diarrhoeas, following category of drugs are used:

**(a) Anti-motility and anti-secretory agents**

These are sub-divided into following sub-classes:

**(i) Opioid agonists:** The drugs in this category are: Loperamide, Diphenoxylate, Difenoxin and Racecadotril. These drugs act by stimulating peripheral μ (mu) as well as δ (delta) receptors of morphine located on small and large intestine. Activation of μ receptor decreases motility; while activation of δ receptor decreases intestinal secretions. For opioid agonists, effects on CNS and dependence liability limit their usefulness.

Loperamide does not cross BBB and has neither analgesic effects nor addiction liability. As an anti-diarrhoeal, it is 40 times more potent than morphine. The usual adult dose is 4 mg followed by 2 mg after each loose motion to a maximum of 16 mg/day. It has onset of action of 1-2 hours and duration of 6-12 hours. For chronic diarrhoea, it is given in the dose of 2-4 mg TDS.

Diphenoxylate or its active metabolite, Difenoxin are other opioid agonists without analgesic actions. However, higher doses have CNS depressant effects and dependence liability after prolonged use. It is less potent than Loperamide. Diphenoxylate (2.5 mg) is usually given along with Atropine (0.025 mg) to discourage abuse potential. It is available as

Lomotil. Atropine, besides providing anti-spasmodic effects, prevents possible abuse of Diphenoxylate because undesirable effects of Atropine would appear prior to anti-motility effects of Diphenoxylate, if the dose is increased for abuse. Usual dose is 2 tablets TDS or QID.

These drugs are useful for traveller's diarrhoea or to prevent non-specific diarrhoea; however oral rehydration therapy (ORT) continues to be main therapy.

These drugs can cause abdominal discomfort and dry mouth. They should not be used in patients with colitis in order to avoid development of megacolon. They should be avoided in patients with acute bacterial diarrhoea associated with high fever or blood in stool, because they may promote systemic invasion due to these microorganisms. they should not be used for children below 2 years of age due to fear of paralytic ileus.

Racecadotril is enkephalinase inhibitor and increases local concentration of enkephalins in intestinal mucosa which then stimulate μ and δ opioid receptors to produce anti-diarrhoeal effects. However its anti-secretory effects are more pronounced than anti-motility effects. usual adult dose is 100-300 mg TDS. Side effects include nausea, constipation and headache. it is secreted through breast milk and hence should be avoided in lactating mothers.

**Preparations:**

- Loperamide: 2 mg tab: **Ridol, Lopamide, Imodium;** 5 mg tab: **Lomin**
- Diphenoxylate: (Diphenoxylate 2.5 mg + Atropine 0.025 mg): **Lomotil;** (Diphenoxylate 2.5 mg + Atropine 0.025 mg + Furazolidone 50 mg) tab: **Lomofen**
- Racecadotril: 100 mg cap: **Racy, Aquasec, Lomorest, Redotil**

**(ii) Anticholinergics:** Anti-cholinergic drugs like Hyoscyamine and Dicyclomine decrease bowel motility and result in an increase of fluid absorption, back from the intestinal tract and also decrease abdominal cramps. However these drugs are usually used in combination with adsorbants or opiates. Adverse effects include dry mouth, blurred vision etc.

**Preparations:**

- Dicyclomine: 10 mg tab: **Colinet;** 10 mg/ml injection: **Cyclopam; (**Dicyclomine 20 mg + Paracetamol 500 mg**)** tab: **Colimex;** (Dicyclomine 10 mg + Mefenamic acid 250 mg) tab: **Meftal-spas**

**(iii) $\alpha_2$-adrenergic receptor agonists:** Clonidine, when given in a dose of 0.1 mg BD orally, facilitates absorption, inhibits secretion of fluids and electrolytes and increases intestinal transit time. Clonidine and substitutes have a role in treatment of diabetic diarrhoea and diarrhoea caused by opiate withdrawal. However its blood pressure lowering effects are major limiting factor in its use as anti-diarrhoeal agents.

**Preparations:**

- Clonidine: 100 μg tab: **Arkamin;** 150 μg tab: **Catapress**

**(iv) Octreotide:** It is a synthetic octapeptide (8 amino acids) with action similar to Somatostatin. It has a longer half life (1.5-2 hours) as compared to Somatostatin (3 minutes).

It inhibits the secretion of growth hormone, glucagon, insulin and VIP. However, its anti-diarrhoeal effects involve inhibition of release of 5-HT, gastrin, secretin, CCK, motilin and pancreatic polypeptide. It reduces GIT motility, intestinal fluid and electrolyte secretion, pancreatic secretion and gall bladder contractions. It is mainly used to treat secretory diarrhoeas associated with carcinoid tumours and VIP-secreting tumours as well as to treat acromegaly and to prevent variceal bleeding, since it decreases hepatic blood flow. It is given subcutaneously in a dose of 100 µg BD or TDS. In low doses of 50 µg subcutaneously, it stimulates GIT motility. A short term therapy causes nausea, abdominal discomfort and pain at the site of injection. Long term therapy can lead to gall stone formation and hypothyroidism. Impaired pancreatic secretion may cause steatorrhoea which can lead to fat-soluble vitamin deficiency.

**Preparations:**

- Octreotide: 50 µg and 100 µg injection: **Octride, Sandostatin, Octate**

**(v) Adsorbant drugs:** Two commonest preparations in this category are Kaolin-pectin combination and Bismuth subsalicylate.

Kaolin is a hydrated magnesium-aluminium silicate while pectin is a indigestible purified carbohydrate obtained from apple. Both agents are combined. They adsorb bacteria, entero-toxins and fluid to increase the consistency of faecal matter. Pectin being a demulscent, coats the inflamed GIT mucosa. It is relatively less used now.

Bismuth subsalicylate reduces stool frequency and liquidity in acute diarrhoea due to inhibition of PG synthesis and chloride secretion due to salicylate content. Bismuth has some antimicrobial effects, binds to enterotoxins and provides protective coating over inflamed gastric mucosa. It is given in a dose of 524 mg (30-60 ml) every 6 hours daily to control traveller's diarrhoea. For acute diarrhoea doses may be increased up to 8 doses per 24 hours. It is rarely used now because of frequent administration.

No adsorbant drug should be taken within two hours of other medication which acts systemically, because it may decrease the absorption of orally administered drugs.

**(vi) Probiotics:** *Lactobacillus sporogens* are intended to replace the normal bacterial flora lost during acute diarrhoea or due to use of antibiotics. These are also used as an adjuvant therapy for aphthous stomatitis and diarrhoea.

**Preparations:**

- Lactobacillus + vitamin B complex: **Capsules of Becelac, Lactobion, Zyspore, Vizylac.**
- High potency probiotics: (*Streptococcus fecalis* T-110 + *Lactobacillus sporogens* + *Clostridium butyricum* + *Bacillus mesentricus* TO-A) cap: **Vizyl, Bifilac-HP;** (*Lactobacillus acidophilus* + *Lactobacillus rhamnosus* + *Bifidobacterium longum* + *Saccharomyces boulardii* + *Streptococcus thermophilus* + fructo oligosaccharides) cap: **Bioform, Vitagut.**

Lactase is indicated for individuals who have insufficient amount of lactase in small intestine. It is an enzyme responsible for digesting lactose, a common disaccharide present in the dairy products. In absence of lactase, lactose draws water into GIT and causes diarrhoea. The dose is 1-2 capsules of lactase with milk.

**(b) Oral Rehydration Therapy (ORT):**

During diarrhoea, a glucose-coupled sodium transport continues in the intestines which causes water and electrolyte losses through stools. Hence glucose-electrolyte solutions are simple, effective and cheaper oral therapy to treat a vast majority of watery diarrhoea. However, if fluid loss is severe and/or severe vomiting persists, then there may be need of intravenous fluids before oral maintenance rehydration therapy. Oral rehydration solution (ORS) replaces the fluid or electrolytes which the body has lost during diarrhoea. The glucose-based ORS can be easily prepared at home as per WHO standard formula, given below.

| | |
|---|---|
| Sodium chloride | 3.5 gm |
| Potassium chloride | 1.5 gm |
| Sodium citrate | 2.9 gm |
| Glucose | 20.0 gm |
| Water | 1 L |

Total osmolarity is 311 mmol/L.

The higher sodium content of WHO formulation is based on approximate sodium loss in adult diarrhoea. However, low-sodium glucose-based formulations may be preferred in infants and children whose faecal losses of sodium are less. The WHO has recommended the replacement of standard 311 mmol/L formula by the new 245 mmol/L formula.

| | |
|---|---|
| Sodium chloride | 2.6 gm |
| Potassium chloride | 1.5 gm |
| Sodium citrate | 2.9 gm |
| Glucose | 13.5 gm |
| Water | 1 L |

For mild to moderate diarrhoea in adults, approximately 2-3 litres of any one of the cited above should be consumed within first 4 hours. Thereafter, the ongoing losses should be replaced.

Carbonated soft drinks, tea, coffee, powdered drinks and hypertonic juices should be avoided in diarrhoea because they make diarrhoea worse and do not contain needed electrolytes.

The cereal-based ORS has the advantage of controlling diarrhoea more effectively than the glucose-based ORS. This is because undigested starch is fermented in the colon to short chain fatty acids which stimulate sodium and water absorption back from the colon. Further, rice powder has 7% protein which on hydrolysis yields amino acids which also stimulate colonic salt and water absorption. The commonly used rice-based ORS has following formula:

| | |
|---|---|
| Pre-cooked rice flour | 10.15 gm (extruded) |
| Sodium chloride | 0.94 gm |
| Sodium citrate | 0.20 gm |
| Potassium citrate | 0.44 gm |
| Water | 200 ml |

**Preparations:**

- Glucose-based ORS: **Relyte** (1 sachet to be dissolved in 200 ml water); **Peditral, Genlyte** (1 sachet to be dissolved in 1 L of water).
- Higher sodium content ORS: **Electral multi-dose, Punarjal, Electrokind** (1 sachet to be dissolved in 1 L of water).
- Rice-based ORS: **Cerelyte, Ricetral** (1 sachet to be dissolved in 200 ml of water)

## 1.9 APPETITE STIMULANTS

Appetite means a desire to eat or drink. It is a complex phenomenon influenced by several factors involving afferent neurons, hormones and metabolites.

Loss of appetite is a common complaint. Its etiology is often vague and varies from prolonged debilitating illness to purely psychological disturbances like depression. Loss of appetite is called as anorexia.

Temporary anorexia due to short illnesses is usually corrected by treatment of the disease entity. Symptomatically, appetite can be improved by varying the diet and using simple preparations like lemon pickles, bitters like bitter orange pill, cardamom and soups. The aromatic bitters combine the property of bitterness and that of an aromatic volatile oil. For example, orange and cardamom. Use of costly appetite stimulants and tonics is unnecessary.

Alcohol in small quantities can augment gastric acid secretion, both reflexly by stimulation of the taste buds and by a direct action. However repeated ingestion of alcohol in high concentration causes chronic gastritis and reduces appetite. Their prolonged use is to be discouraged because of well known addiction liability.

Insulin, on parenteral administration augments gastric secretion by producing hypoglycaemia; however its use for stimulating appetite is irrational and hazardous.

5-HT antagonists, **Cyproheptadine** has also been considered to have appetite stimulating property; however its use in large doses inhibits release of ACTH and depress the circulating levels of cortisol. Indiscriminate use of such drugs for stimulating appetite should be avoided.

## 1.10 APPETITE SUPPRESSANTS

Indirectly acting sympathomimetics like Amphetamine and its derivatives Fenfluramine or Dexfenfluramine were used earlier as appetite suppressants to treat obesity. Although Amphetamine and its derivatives have a significant anorexic (appetite suppresant) effect, tolerance to this action develops within few weeks and the food intake returns to normal. In addition adverse effects like insomnia, pulmonary hypertension and the abuse potentials

have discouraged their use in weight control. Hence their use as appetite suppressant is now discarded.

A new drug **Sibutramine** is used for the management of obesity. It blocks the neuronal uptake of mainly nor-epinephrine, 5-HT and also dopamine at the hypothalamic site which regulates food intake. It can be used in severely obesed patients with other risk factors such as diabetes and dyslipidaemia. It reduces food intake and causes dose-dependent weight loss with reduction in visceral fat. In addition, it decreases plasma triglycerides, LDL, VLDL but increases HDL. It also stimulates thermogenesis by activating $\beta_3$ receptors in adipose tissue. Usual oral dose is 10-15 mg once daily.

Adverse effects include dry mouth, headache, insomnia, constipation, increase in heart rate and blood pressure. The drug is contraindicated in any kind of cardiovascular disease. It should not be taken along with SSRIs like Fluoxetine, serotonin-antagonists like Sumatriptan and Lithium.

**Preparations:**

- Fenfluramine : 20 mg tab, 40 mg cap: **Flabolin**
- Sibutramine: 5 mg, 10 mg cap: **Obego, Obestat, Sibutrex**

## 1.11 DIGESTANT DRUGS

These are the drugs which are claimed to aid digestion in the GIT. Following drugs are used as Digestants:

**(1) Pepsin:** It is a proteolytic enzyme. It is administered orally in a dose of 0.5-1 gm. It is of doubtful value except in patients with gastric achylia, a condition characterised by defective acid and pepsin secretion by the stomach. Gastric achylia is observed in patients with carcinoma of the stomach and pernicious anaemia.

Another enzyme called papain, obtained from vegetable source ie papaya, has also proteolytic property.

**(2) Rennin:** It is a partially purified milk- curdling enzyme. It is employed for similar purpose like pepsin. It is used in the preparation of cheese.

**(3) Pancreatin:** It contains the enzymes amylase, trypsin and lipase. It is employed as a replacement therapy in chronic pancreatitis, an obstruction caused by cancer of head of pancreas, cystic fibrosis, and after total gastrectomy and pancreatectomy. It is not useful in GI disorders unrelated to pancreatic enzyme insufficiency. It is administered orally in the form of enteric coated capsules, to prevent its gastric inactivation. Since the content of enzymes in a tablet or capsule is much less as compared to quantities needed for efficient digestion. As a result, large doses are needed to be prescribed with meals. Even with high doses, total correction of steatorrhoea may not occur. Hence, pancreatin should be used only as an adjunct to reduction in dietary fat intake. Prolonged use of pancreatin can cause fibrosing colonopathy.

**(4) Bile and bile acids:** About 1 L of bile is secreted daily by the liver cells. It contains bile acids, cholesterol and bilirubin. They are important in emulsifying the fats in the intestine.

Cholecystokinin (CCK) is a polypeptide secreted by the duodenal mucosa. It is the main stimulant for biliary secretion. However it is not available for therapeutic use. Bile salts increase the flow as well as the concentration of bile and hence they are termed as choleretics. The bile salts and acids do not increase the excretion of performed bile pigments.

The bile salt preparations have been employed to facilitate surgical drainage, as replacement therapy in biliary fistulae. They are also used for their choleretic effect in conditions like liver cirrhosis and functional hepatic insufficiency.

**Preparations:**

- Dehydrocholic acid: 250 mg tab
- Sodium dehydrocholate injection: 20% solution in 3 and 10 ml ampoules (IV)
- Caerulein, a polypeptide which is 3 times more active than CCK.

**(5) Chenodeoxycholic acid (CDCA, Chenodiol, Chenofalk):** It is the normal constituent of bile. When given orally, it is useful in dissolving gall stones and in preventing their recurrence. It reduces biliary cholesterol concentration by depressing hepatic cholesterol secretion. It increases the secretion of bile acids in some patients. It dissolves radiolucent gall stones but it is ineffective with the radio-opaque ones. The results are poor in presence of a non-functioning gall bladder, in very obese patients, in persons with high dietary cholesterol intake and in those receiving drugs like Clofibrate or Octeotride. It is given orally in a dose of 10-15 mg/Kg/day as a single dose at bed time. It needs to be administered for a long time like 3-24 months depending on the size of stone. The drug causes adverse effects like diarrhoea, increase in the LDL cholesterol and rarely hepatotoxicity.

**(6) Ursodeoxycholic acid (Ursodiol, Udiliv):** It is an analogue of CDCA. It has action similar to that of CDCA, but it does not increase excretion of bile acids into bile. Given orally, it is absorbed rapidly and is taken up by the liver. Adverse effects are less severe than that of CDCA.

Ursodiol is given orally in a dose of 13-15 mg/Kg/day in divided doses. It shows clinical, biochemical and histological improvement in primary biliary cirrhosis. It acts by modifying the composition of bile acids in the liver, thereby hindering the progression of the pathological process to the terminal stage. It also lowers levels of serum cholesterol in these patients.

## 1.12 CARMINATIVE DRUGS

These drugs are used to expel gas from the stomach or intestines in the treatment of flatulence and colics. Most of these drugs are aromatic volatile oils. They act by mild irritation, thereby increasing the GIT motility and causing relaxation of sphincters. They produce a feeling of warmth in the stomach. They do not affect the gastric acid secretion significantly. The commonest spices in Indian food which contains carminative components are cardamom seeds, ginger, fennel seeds, asafoetida, cinnamon bark, cloves, coriander and anise. Therapeutically, these volatile oils are used in the form of tinctures like tincture cardamom or tincture zingiberis.

Although carminatives may offer symptomatic relief and audible satisfaction, it is to be noted that flatulent dyspepsia may be associated with disorders like peptic ulcer, biliary tract disease, irritable bowel syndrome and even ischaemic heart disease.

**Dimethylpolysiloxane (Dimol),** is a silicon derivative advocated in symptomatic relief of post-prandial and post-operartive flatulence and abdominal distention. It eliminates mucus-embedded bubbles which interfere with visualisation during gastroscopy. It is not much effective in reducing gas which may interfere with radiologic or ultrasound examination of the abdomen. It acts as a defoaming agent, allowing the gas to escape from GIT and provides comfort to the patient. It is available as 40 mg tablets. It is also used in combination with antacids, antispasmodics and Digestants.

## 1.13 EMETIC DRUGS

Emesis means vomiting. Vomiting refers to expulsion of gastric contents through mouth due to mass anti-peristalsis. It is usually preceded by nausea which means an uneasy feeling in anticipation of vomiting. Vomiting results due to stimulation of vomiting centre, which is located in the lateral medullary reticular formation.

Emetics are used for deliberate production of emesis for treatment. They may act centrally by stimulating chemoreceptor trigger zone (CTZ) or may work as reflex emetics. Commonly used emetics are Apomorphine and Ipecacuanha. Apomorphine is a semi-synthetic morphine derivative which stimulates dopamine receptors at CTZ. It is administered parenterally, sub-cutaneously or intramuscularly. If vomiting does not occur, then second dose should be avoided. Larger doses produce convulsions and respiratory depression.

Ipecacuanha, in the form of syrup of Ipecac is produced from the roots of *Cephalis cuanha*. It stimulates CTZ and also works as a reflex emetic. Its active principle is Emetine. It is administered orally and is safer than Apomorphine. Ingestion of sodium chloride powder or solution and mustard powder also serve as domestic emetics.

Emetics are contraindicated in hypertension, peptic ulcer, pulmonary tuberculosis, uraemia and pregnancy. Emetics should be avoided in case of corrosive poisons because an increase in intragastric pressure may cause perforation. Emetics should be avoided in cases of poisoning due to petroleum products because of danger of lipoid aspiration pneumonia.

## 1.14 ANTI-EMETIC DRUGS

There are different causes of emesis. Use of anti-emetic drugs depends on the cause.

**Types of Emesis:**

There are four types of emesis:

**(1) Motion sickness:** It can result during space flights, taking off and landing of an aeroplane, viewing of a moving horizon or waves of deep sea from the dock of a rolling ship. Even travel on the land when the route is circular with acute contours can cause emesis. It is a labyrinthine vomiting via stimulation of vestibular nuclei.

Use of histamine $H_1$ receptor antagonists or centrally acting anti-cholinergic drugs is preferred.

$H_1$ antagonists, with anti-cholinergic properties are particularly useful in this condition. The examples are Diphenhydramine, Dimenhydrinate, Cyclizine or Meclizine most commonly preferred for treatment of vertigo due to labyrinth dysfunction. Another drug in this category is Promethazine. These drugs are associated with common anti-cholinergic side effects like dry mouth, blurred vision, tachycardia and also sedation. Cinnarizine is an anti-histamine with additional anti-cholinergic, anti-serotonin and $Ca^{++}$ channel blocking properties. By inhibiting the influx of $Ca^{++}$ from endolymph into the vestibular apparatus, it blocks further mediation of labyrinthine reflexes.

The example from the category of centrally acting anti-cholinergics is of Hyoscine (Scopolamine). It is used in the form of a transdermal patch or 0.6 mg oral form, 30-60 minutes before journey. It can also be used prophylactically. 0.2 mg of intramuscular injection can also be given when the motion sickness has started. Side effects include blurred vision, dryness of mouth, cycloplegia, sedation and sleepiness.

**Preparations:**

- Diphenhydramine : 25 mg tab, 12.5 mg/ml syrup: **Benadryl**
- Dimenhydrinate: 50 mg tab, 15.63 mg/ml syrup, 50 mg/ml injection: **Dramamin**
- Meclizine: (Meclizine 25 mg + Caffeine 20 mg) tab: **Pregnidoxin**
- Promethazine: 25 mg tab: **Avomine,** 10 mg, 25 mg tab, 5 mg/5 ml syrup: **Phenergan**
- Cinnarizine : 25 mg, 75 mg tab: **Stugeron, Cinzan**

**(2) Morning sickness (vomiting during pregnancy):** It results in the first trimester of pregnancy due to effect of increased levels of estrogen on CTZ. The effect persists for few weeks and then subsides. During this condition, as far as possible drugs should be avoided. However in some cases hyperemesis can lead to dehydration, which needs proper treatment.

Amongst anti-histamines, Doxylamine, Cyclizine or Meclizine can be used. Out of these drugs, Doxylamine (Doxinate) is the safest and has no teratogenic potential. In addition, vitamin $B_6$ (Pyridoxine) in high doses of 20-60 mg/day is effective. Vitamin $B_6$ serves as a cofactor for the enzyme glutamate decarboxylase and increases the synthesis of GABA. It is reported that GABA has inhibitory effect on CTZ.

**Preparations:**

- Doxylamine: (Doxylamine 10 mg + Pyridoxine 10 mg) tab: **Vominate, Vomena**

**(3) Chemotherapy or radiation-induced emesis:** Anti-cancer drugs like Cisplatin induce emesis by directly activating 5-$HT_3$ receptors in CTZ or may bind to vagal and splanchnic 5-$HT_3$ receptors to send emetogenic signals. In this case, 5-$HT_3$ antagonists like Ondansetron, Granisetron, Dolasetron, Tropisetron and Palonosetron are useful.

These drugs are given by intravenous route as a single dose, 30 minutes prior to chemotherapy. The doses are: Ondansetron: 0.15 mg/Kg, Dolasetron: 1.8 mg/Kg, Granisetron: 10 µg/Kg (?) and Palonosetron: 0.25 mg. Palonosetron is most potent with a half life of 40 hours. If needed, these drugs may be repeated (except Palonosetron) every 24 hours. For less emetogenic chemotherapeutic agents used in radiotherapy, oral doses of Ondansetron 8 mg BD, Granisetron 2 mg/day or Dolasetron 100 mg/day can be used.

The efficacy of 5-$HT_3$ antagonists is enhanced by concurrent administration of Dexamethasone or Prochlorperazine/Metoclopramide/ Domperidon and/or Diazepam. These drugs may cause headache, constipation, abdominal discomfort and rashes. Dolasetron may prolong QT interval and should be avoided in patients with prolonged QT.

Earlier, Metoclopramide was the most commonly used anti-emetic drug for treating chemotherapy/radiation induced nausea-vomiting. It was given orally in a dose of 5 mg TDS or intramuscularly every 6 hours. In addition to Dopamine, $D_2$ receptor blocking action on CTZ, it also has a prokinetic effect. It is combined with other agents like Diphenhydramine (histamine $H_1$ blocker), Dexamethasone (a corticosteroid) and Lorazepam/Diazepam (anti-anxiety agent).

Domperidon in a oral dose of 10-40 mg TDS, is another Dopamine $D_2$ antagonist. It is less effective than Metoclopramide. It has relatively less CNS side effects like restlessness, dystonias and Parkinson-like symptoms because of poor penetration to CNS. It is usually combined with Prochlorperazine, Diphenhydramine and Dexamethasone.

**Preparations:**

- Ondansetron: 4 mg, 8 mg tab, 2 mg/ml injection: **Zofar, Zondan, Emeset, Ondem;** 4 mg tab, 2 mg/5 ml syrup, 2 mg/ml injection: **Naucid, Vomikind**
- Granisetron: 1 mg, 2 mg tab, 1 mg/ml injection: **Graniset, Cadigran, Grandem**
- Palonosetron: 0.25 mg/5 ml injection: **Palzen, Palnox**
- Metoclopramide: 5 mg, 10 mg tab, 5 mg/5 ml syrup, 5 mg/ml injection: **Perinorm, Reglan, Maxeron**
- Domperidon: 5 mg, 10 mg, 30 mg tab; 5 mg, 10 mg DT-tab, 1 mg/ml suspension, 10 mg/ml drops: **Domperon, Domstal, Motinorm**

**(4) Post-operative Vomiting:** Post-operative nausea-vomiting are complications in patients receiving general anaesthesia. Women undergoing gynaecological surgery are particularly at great risk in experiencing such type of vomiting. 5-$HT_3$ receptor-antagonists like Ondansetron (mentioned above) are generally preferred to prevent or treat post-operative nausea and vomiting. In addition, anti-histamines like Promethazine/Diphenhydramine and pro-kinetic drugs like Metoclopramide/Domperidon are also used for this purpose with a limited success.

Phenothiazines, which are used as anti-psychotic drugs can also be used for their anti-emetic properties in post-operative nausea and vomiting. The most commonly used agents are Prochloperazine, in an oral dose of 5-25 mg TDS or 12.5 mg intravenous or Promethazine, in an oral dose of 12.5-25 mg BD or TDS are used for this purpose. Prochlorperazine has dopamine $D_2$ receptor and muscarinic receptor blocking action. Promethazine is a potent anti-histamine and anti-cholinergic drug.

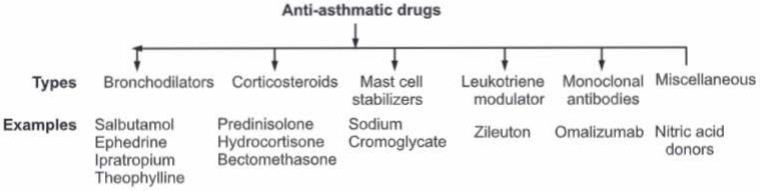
Anti-psychotics, belonging to butyrophenone group, like Droperidol can be used to treat post-operative nausea and vomiting by giving intramuscular or intravenous injection.

Droperidol can cause sedation. Both Prochlorperazine and Droperidol can precipitate extra-pyramidal side effects and postural hypotension. Droperidol should not be used in patients showing QT prolongation in ECG.

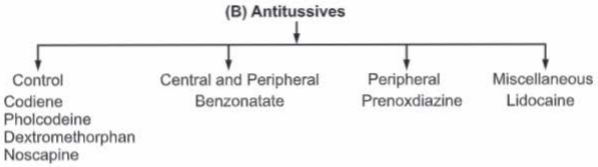
**Preparations:**

- Prochlorperazine: 5 mg tab, 12.5 mg/ml injection: **Stematil, Emidoxyn, Vometil**
- Droperidol: 2.5 mg/ml injection: **Droperol**
- Promethazine: 25 mg tab: **Avomin;** 10 mg, 25 mg tab, 5 mg/5 ml syrup: **Phenergan**

## SUMMARY

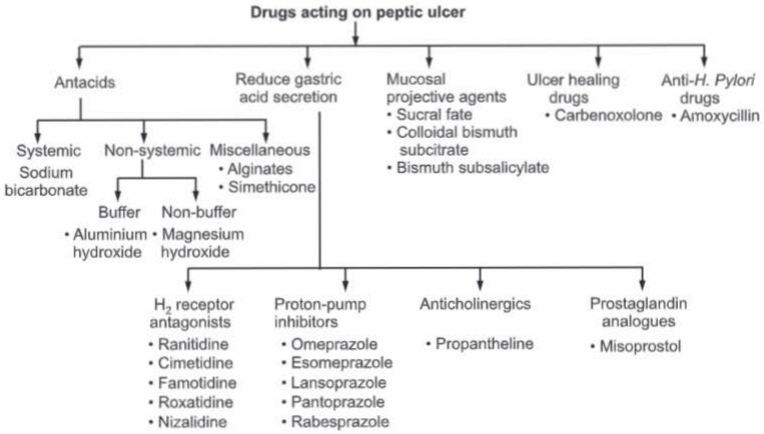


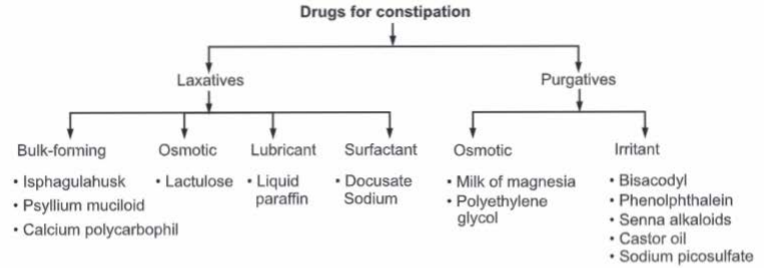

**Drugs for COPD**
Theophylline
Prednisolone
Oxygen

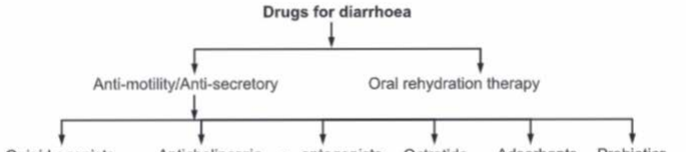




**Nasal decongestants**
Naphazoline
Oxymatazoline
Xylometazoline
Pseudoephedrine

**Respiratory stimulant**
Doxapram


Drugs acting on peptic ulcer
Antacids
Reduce gastric acid secretion
Mucosal projective agents
• Sucral fate
• Colloidal bismuth subcitrate
• Bismuth subsalicylate
Ulcer healing drugs
• Carbenoxolone
Anti-H. Pylori drugs
• Amoxycillin
Systemic
Sodium bicarbonate
Non-systemic
Miscellaneous
• Alginates
• Simethicone
Buffer
• Aluminium hydroxide
Non-buffer
• Magnesium hydroxide
H2 receptor antagonists
• Ranitidine
• Cimetidine
• Famotidine
• Roxatidine
• Nizalidine
Proton-pump inhibitors
• Omeprazole
• Esomeprazole
• Lansoprazole
• Pantoprazole
• Rabesprazole
Anticholinergics
• Propantheline
Prostaglandin analogues
• Misoprostol


Drugs for constipation
Laxatives
Purgatives
Bulk-forming
• Isphagulahusk
• Psyllium muciloid
• Calcium polycarbophil
Osmotic
• Lactulose
Lubricant
• Liquid paraffin
Surfactant
• Docusate Sodium
Osmotic
• Milk of magnesia
• Polyethylene glycol
Irritant
• Bisacodyl
• Phenolphthalein
• Senna alkaloids
• Castor oil
• Sodium picosulfate



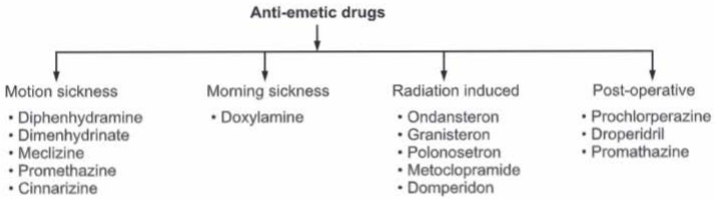

**Appetite stimulants**
- Cyproheptadine

**Appetite suppressants**
- Sibutramine
- Fenfluramine

**Digestant drugs**
- Pepsin
- Rennin
- Pancreatin
- Bile and bile acids
- Chenodeoxycholic acid
- Ursodeoxycholic acid

**Carminative drugs**
- Dimethylpolysiloxane

**Emetic drugs**
- Apomorphine
- Ipecacuanha



## REVIEW QUESTIONS

**Long Answer Questions.**

1. Describe Pathophysiology of asthma with an appropriate figure.
2. Classify anti-asthmatic drugs with one example each.
3. Write Pathophysiology of COPD.
4. What are options for treatment of COPD?
5. Differentiate between expectorants and anti-tussives.
6. Classify drugs acting on peptic ulcer with suitable examples.
7. Describe clinical uses, adverse effects and drug interactions of histamine $H_2$ blockers.
8. Describe clinical uses, adverse effects and drug interactions of PPIs.
9. Classify drugs acting on constipation with suitable examples.
10. Classify laxatives and discuss their effects.
11. What is the role of oral rehydration therapy in diarrhoea?
12. Discuss use of anti-emetic drugs.

**Short Answer Questions.**

1. Write short notes on:
   (a) Selective $\beta_2$ agonists
   (b) Salbutamol
   (c) Ephedrine
   (d) Ipratropium
   (e) Theophylline
   (f) Aerosol corticosteroids
   (g) Cromolyn sodium
   (h) Montelukast
   (i) Status asthmaticus
   (j) Mucokinetic expectorants
   (k) Mucolytic expectorants
   (l) Bromhexine
   (m) Misoprostol
   (n) Sucralfate
   (o) *Helicobacter pylori*
   (p) Osmotic purgatives
   (q) Irritant purgatives
   (r) Lomotil
   (s) Kaolin-pectin
   (t) Probiotics
   (u) Sibutramine
   (v) Chenodeoxycholic acid
   (w) Ursodiol
2. What is the mechanism of action of $\beta_2$ agonists?
3. How corticosteroids help in bronchial asthma?

4. What are mast cell stabilisers?
5. What are leukotriene modulators?
6. What are anti-tussives?
7. What are nasal decongestants?
8. What are drug interactions of antacids?
9. What is mechanism of action of Ranitidine?
10. Comment on digestant drugs.
11. What are carminative drugs?
12. What are emetic drugs?

*Unit* ...**2**

# CHEMOTHERAPY - I

Upon completion of this section, the student should be able to

- Comprehend general principles of chemotherapy
- Understand pharmacology of sulphonamides.
- Understand pharmacology of Cotrimoxazole.
- Understand pharmacology of following antibiotics:
  - Penicillins
  - Cephalosporins
  - Chloramphenicol
  - Macrolides
  - Quinolones
  - Fluoroquinolins
  - Tetracyclines
  - Aminoglycosides

## 2.1 GENERAL PRINCIPLES OF CHEMOTHERAPY

Chemotherapy means treatment of systemic/topical infection with drugs which have selective toxicity for an invading pathogen (living or multiplying) without harming host cells. Frequently, the selective toxicity is relative in nature. It takes advantage of the biochemical and physiological differences which exist between microorganisms (prokaryotes) and human beings (eukaryotes).

The term anti-microbial agent includes drugs synthesised in the laboratory as well as those obtained from fermentation by microorganisms. These agents may act either as bacteriostatic or bactericidal. **Bacteriostatic** drugs arrest the growth and replication of the bacteria and thus limit the spread of infection. On the other hand, **bactericidal** drugs kill or irreversibly damage the multiplying bacteria, so that the total number of viable organisms decreases. In case of fungi, the drugs are called as **fungistatic or fungicidal.**

Living organisms are classified as **prokaryotes** (as of bacteria) or as **eukaryotes** (as of mammals, protozoa, fungi and helminths).

**Sites and Mechanism of Action of Antibiotics:**

Antimicrobials affect the viability of microorganisms by four different mechanisms as shown in Fig. 2.1. Drugs which affect bacterial cell wall or membrane integrity and DNA

synthesis are usually (but not always) bactericidal; while those affecting protein and folic acid synthesis are usually (but not always) bacteriostatic.

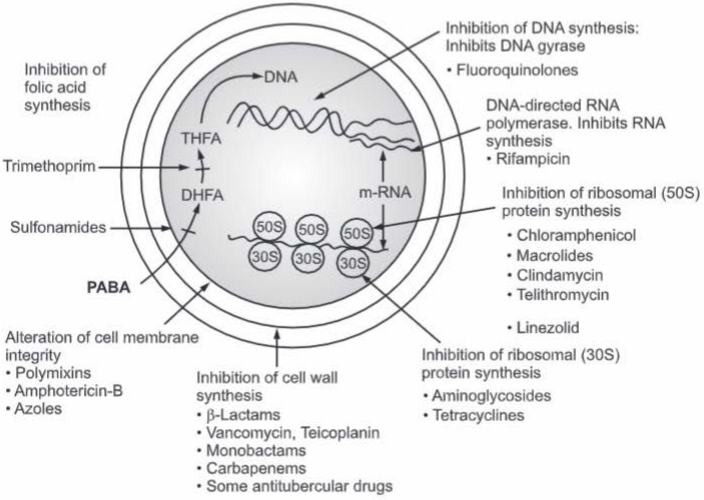



**Fig. 2.1: Mechanisms of action of antibiotics**

- **Inhibition of bacterial cell wall synthesis**

All penicillins, cephalosporins, monobactams and carbapenems inhibit bacterial cell wall synthesis by binding to the one or more of penicillin binding proteins (PBPs), which inhibit the final trans-peptidation step of peptidoglycan synthesis in bacterial cell wall. See Fig. 2.1. The formation of an imperfect cell wall leads to an osmotic drive of the fluid from outside to inside. As a result the bacteria swell and burst to die. The lysis of the bacteria is facilitated by an outgoing activity of cell wall autolysing enzymes.

- **Alteration of cell membrane integrity**

Polymixins function as cationic detergents and disrupt the bacterial cell membrane osmotic integrity by displacing $Ca^{++}$ and $Mg^{++}$ ions from membrane lipid phosphates. This ends up in the leakage of intracellular constituents and the death of bacteria. Some anti-fungal antibiotics like Amphotericin-B bind to ergosterol present in fungal cell membrane and alter its permeability by forming pores through which $K^+$, $Na^+$, $H^+$, and other molecules leak out, leading to cell death. The azole group of anti-fungal drugs also inhibit ergosterol biosynthesis which results in damaged leaky fungal cell membrane.

- **Inhibition of ribosomal protein synthesis**

Ribosomes are involved in the protein synthesis by the bacteria. The bacterial ribosome consists of a 50S and 30S sub-unit which when combined, form 70S sub-unit while in the mammalian ribosomes the 60S and 40S sub-units combine to form 80S sub-unit. This difference provides the basis for selective anti-microbial action of some antibiotics.

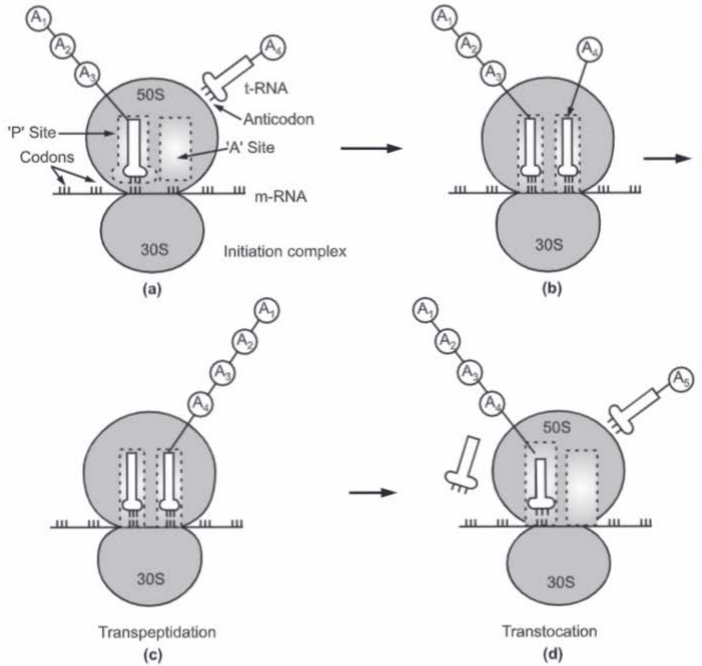



**Fig. 2.2: Protein synthesis in bacteria**

The protein synthesis in bacteria is depicted in Fig. 2.2. It occurs in four steps as follows:

**(a) Step 1:** Messenger RNA (m-RNA) which is transcribed from DNA, becomes attached to 30S sub-unit of the ribosome followed by 50S sub-unit leading to 70S sub-unit. This unit moves along m-RNA so that successive codons of m-RNA pass along the ribosome from the acceptor site (A-site) to the peptidyl site (P-site). This stage is called as formation of initiation complex. Codon means a triplet of three nucleotides carrying the codes for a specific amino acid.

A transfer RNA (t-RNA) with its existing amino acid chain ($A_1$-$A_3$) is already attached at the P- site of the complex by complimentary codon: anticodon pairing. The incoming t-RNA carries another amino acid ($A_4$) to be added to the growing peptide chain.

(b) **Step 2:** The incoming t-RNA with a new amino acid ($A_4$) binds to the acceptor site (A-site) by complimentary base pairing.

(c) **Step 3:** The peptide chain ($A_1$-$A_3$) on the t-RNA attach to the P-site is then transferred to the t-RNA linked to A-site. This process is called as **transpeptidation.** The t-RNA at the P-site has lost its peptide and transferred it to t-RNA of the A-site which now consists of four amino acid peptide chain ($A_1 - A_4$).

(d) **Step 4:** The t-RNA which has lost its peptide chain is then ejected out from the P-site, while the t-RNA at the A-site (with four amino acid chain) is translocated to the P-site. The freed A-site is now ready to receive a new t-RNA, with new amino acid ($A_5$) and relevant anti-codon attached to it. The whole process is then repeated. During the process of **translocation,** the ribosome moves on one codon relative to the messenger. Usually, several ribosomes, termed as polysomes simultaneously translate on a single m-RNA template.

Antibiotics like Aminoglycosides, Macrolides, Chloramphenicol and Tetracyclines act by inhibiting ribosomal protein synthesis at different stages.

- **Suppression of DNA Synthesis:**

The nucleic acid synthesis can be inhibited by five different mechanisms as indicated below:

**Inhibiting the synthesis of folates, purines and pyrimidines:** Human beings cannot synthesise folic acid but acquire it from diet; while bacteria and sexual forms of malarial protozoa cannot make use of preformed folic acid. Bacteria, therefore, synthesise their own folic acid. Tetrahydrofolic acid is essential for the growth of bacteria as it is crucial for one-carbon transfers in nucleic acid synthesis. Sulphonamides are structural analogues of p-amino benzoic acid (PABA) and block the conversion of PABA to dihydrofolic acid by inhibiting the enzyme dihydropteroate synthase. In addition, Trimethoprim blocks the next step ie converting dihydrofolic acid to tetrahydrofolic acid by the enzyme dihydrofolate reductase. See figure 2.1. When the bacteria are deprived of folic acid, their growth caeses. Individually both drugs are bacteriostatic, but when combined together (Co-trimoxazole) they cause a sequential blockade providing a synergistic bactericidal action.

**Altering the base pairing properties of the template:** Some topically applied antiseptics like Acriflavin act by this mechanism. These agents intercalate (get inserted) in the DNA to inhibit its synthesis. Acriflavin, by intercalating, doubles the distance between adjacent base pairs and causes deletion of a base, or an insertion of an extra base or causes mis-pairing between two bases.

**Inhibiting either DNA or RNA polymerase:** DNA-polymerase has a catalysing as well as proof reading function during the synthesis of new DNA strand. RNA polymerase (or DNA dependent-RNA polymerase) synthesises all RNAs in prokaryotes from their DNA; and transcription is a process in which RNA is synthesised from DNA. There are three types of RNAs: m-RNA, t-RNA and r-RNA (ribosomal RNA). The r-RNA is necessary for:

(a) Assembly of ribosomes.

(b) Binding of m-RNA to the functional ribosomal units, and

(c) For peptidyl chain transfer process in the ribosomes.

All these steps are essential in protein synthesis by bacteria. See figure 2.2. Some of the antibiotics act by inhibiting either DNA or RNA polymerase.

**Inhibiting DNA gyrase:** During replication stage of DNA synthesis, as the double helical strands of DNA separate from one end, the positive super coils (over binding) are formed at the other end. The problem of super coiling which comes in the way of bacterial DNA replication is overcome by a group of enzymes called DNA topoisomerases (DNA gyrase).

In Gram-negative bacteria, DNA gyrase (topoisomerase II) is responsible for continuously introducing negative supercoils into DNA. Its function is to cut both the strands of bacterial DNA and then reseal them to overcome the process of supercoiling. In Gram-positive bacteria, this problem is overcome by topoisomerase IV. It separates the interlinked daughter DNA molecules and then reseals the strands. Fluoroquinolone antibiotics block the cutting and resealing activity of DNA gyrase and also block the delinking action of topoisomerase IV.

**Directly damaging DNA and its functioning:** Many anti-cancer drugs make a covalent bonding with the bases of DNA and prevent their replication. Metronidazole partly acts by this mechanism.

**BACTERIAL RESISTANCE TO ANTIBIOTICS**

The population of most of the bacteria gets doubled in just 30 minutes. Hence within few hours, there are several generations; which provides an opportunity for genetic adaptations. It can lead to drug resistance, which refers to unresponsiveness of microorganisms to an antimicrobial agent after its repeated use. Another term, called as tolerance refers to increase in the dose in order to produce the same pharmacological response of equal magnitude and duration. The term "**antibiotic tolerance**" is used when the antibiotic no longer kills the microorganism but merely inhibits its growth or multiplication. Tolerant microorganisms start to grow after the antibiotic is stopped, while resistant microorganisms multiply even in the presence of antibiotics.

Antibiotic resistance could be intrinsic (natural) or acquired. The acquired resistance develops due to widespread and irrational use of antibiotics. This type of resistance develops either by gene transfer or by mutation or by modification in biochemical mechanisms. The mechanisms are discussed below:

- **Genetic methods of antibiotic resistance**

These are exhibited by two mechanisms: chromosomal and extra-chromosomal.

**Chromosomal methods: Mutations :** Mutation refers to a change in DNA structure of a gene. The spontaneous mutation in bacterial cells occurs at a frequency of about one per million cells. During therapy of antibiotic, sensitive bacteria may die but the resistant ones continue to grow resulting in "selection of mutants". Such mutants confer resistance to the antibiotic. Such mutants create a big clinical problem, especially in mycobacteria (tuberculosis and leprosy) and in *Staphylococcus aureus* by forming methicillin-resistant organism (MRSA).

- **Extra-chromosomal mechanisms: Plasmids :** Plasmids are extra-chromosomal genetic materials which can replicate independently and freely in cytoplasm. Plasmids which carry genes resistance to antibiotics (r-genes) are called as R-plasmids. These r-genes can be readily transferred from one R-plasmid to another plasmid or to chromosome. Much of the drug resistance encountered in clinical practice is plasmid mediated. It is exerted by two mechanisms: from one bacterium to another or between plasmids of the same bacteria.

**(A) From One Bacterium to Another**

The transfer of resistant genes can occur between bacteria of the same species. It occurs through any one of the following three methods:

**(a) Conjugation:** It is the main mechanism for the spread of resistance or even multi-drug resistance. The conjugative plasmids containing the transfer r-genes, make a connecting tube between two bacteria through which the plasmid passes. This is commonly observed with bacterial population at high density, as in GIT because the resident micro-flora can serve as a reservoir for the resistant genes which can be transferred to other organisms which later invade the host.

**(b) Transduction:** It is relatively less common method of transfer of resistance. During transduction, the plasmid DNA in a bacterial virus (bacteriophage) is transferred to another bacterium of the same species. It is usually observed in the transmission of resistant genes between strains of staphylococci and that of streptococci.

**(c) Transformation:** This method is of minimal clinical relevance. It involves the ability of certain bacteria to pick up free DNA from the environment i.e from a cell belonging to closely related or the same strain. The new DNA is then incorporated into the genome of the bacteria which then becomes resistant.

Genetic methods of antibiotic resistance are depicted in Fig. 2.3.

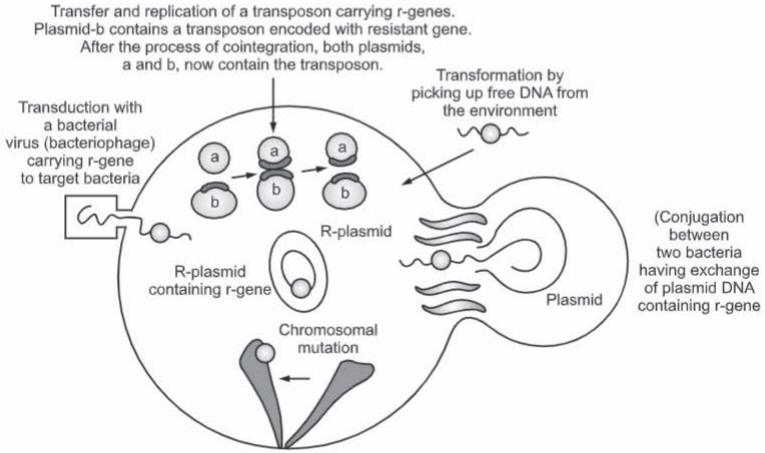



**Fig. 2.3: Genetic method of antibiotic resistance**

**(B) Between Plasmids of the Same Bacterium**

Transfer of r-genes between plasmids within the bacterium can occur through following two means:

**(a) By transposons:** These are DNA segments which cannot self-replicate but can self-transfer between plasmids or from plasmid to chromosome. In this process, the donor plasmid, containing a transposon, co-integrates with the acceptor/target plasmid. During the process of co-integration, the transposon can now replicate. Both the plasmids then separate and each one of them contains the r-gene carrying the transposon. See figure 2.3. Some strains of staphylococci and enterococci acquire resistance transferred by transposons. As a result, these organisms can cause virtually untreatable nosocomial (hospital acquired) infections.

**(b) By integrons:** A larger mobile DNA unit is called as integron, which can be located on a transposon. Multi-drug resistance is usually transmitted by integrons. Each integron is packed with multiple gene cassettes, each consisting of a resistant gene attached to a small recognition site. These gene cassettes are encoded with several bacterial functions including resistance and virulence. Gene cassettes have been identified for many antibiotics except for Fluoroquinolone. Integrons cannot promote self-transfer because they lack transporter genes, but are commonly associated with and work with tranposons and conjugative plasmids.

- **Biochemical Mechanisms of Resistance to Antibiotics**

These occur through following five mechanisms:

**(A) An enzyme inactivating the antibiotics:** This is experienced in β-lactum antibiotics, Chloramphenicol and aminoglycoside antibiotics.

*Staphylococcus aureus, Neisseria gonorrhoea, Haemophylus influenza* and some enteric Gram-negative rods produce the enzyme β-lactamase which cleaves the β-lactum ring and inactivates the antibiotic. However, some β-lactumases have a preference for penicillins while few others have preference for cephalosporins. Thus the cross-resistance is not complete. Newer β-lactum antibiotics like mono-bactums and carbapenems as well as third/fourth generation cephalosporins are resistant to these enzymes.

Chloramphenicol is inactivated by the enzyme Chloramphenicol acetyl transferase produced by resistant strains of Gram-negative and Gram-positive bacteria. The r-genes are borne on plasmids. See Fig. 2.4. The Gram-negative bacteria exhibit five-fold higher resistance as compared to Gram-positive bacteria, because in case of Gram-negative bacteria the enzyme is present constitutively while in Gram-positive bacteria this enzyme is inducible.

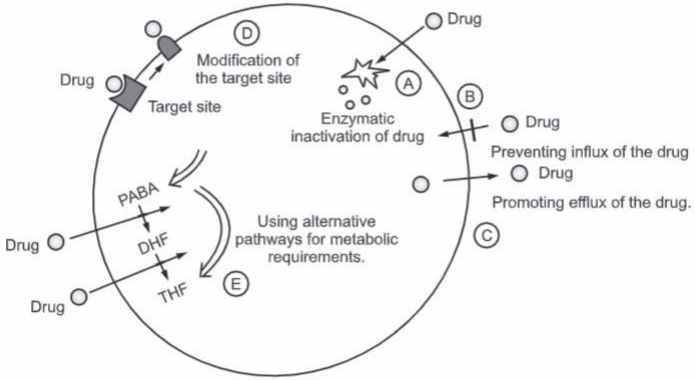



**Fig. 2.4: Mechanism of bacterial residence**

Aminoglycosides are inactivated by acetyl transferases, phosphotransferases and adenyl transferases present in both in Gram-negative and Gram-positive organisms. The resistant genes are carried on plasmids and also on transposons. See Fig. 2.4 A.

**(B) Prevention of drug accumulation in the bacterium:**

The bacterial membrane may undergo biochemical alteration, either by not allowing influx or by promoting efflux of the drug. Efflux pumps are membrane transport proteins in the cytoplasm. An example is of P-glycoprotein which commonly operates in *E coli, P aeruginosa, S typhi, S. aureus, S. pyogenes, S. pneumonia, N gonorrhoea* and mycobacteria

as well as enterococci. These chromosomal or plasmid-mediated efflux transporter proteins protect the bacterial cell from foreign chemical invasion and are regulated by a number of genes.

This mechanism is observed in case of tetracyclines, fluoroquinolones and erythromycin. Some Gram-negative bacteria inhibit plasmid-mediated synthesis of porin channels, which obstructs influx of antibiotics like Ampicillin. Mutations in the membrane have been reported to reduce accumulation of tetracyclines, Chloramphenicol, Aminoglycosides and β-lactum antibiotics. See figure 2.4 B and C.

**(C) By Modification/Protection of the Target Site:**

Sometimes target sites are altered to exert resistance. The example is of ribosomal point mutations offering resistance to tetracyclines, Macrolides and Clindamycin. DNA gyrase and topoisomerase is altered in case of Fluoroquinolones. Penicillin-Binding-proteins (PBPs) are modified in case of *Strepto pneumonia* leading to Penicillin resistance. Point mutation means replacement of only one base pair in DNA. See figure 2.4 D.

**(D) Use of Alternative Pathways for Metabolic/Growth Requirements:**

Resistance also can occur by developing an alternative pathway which bypasses the reaction inhibited by the antibiotic. Thus sulphonamide resistance may occur from over-production of PABA and some enteric organisms evade β-lactum antibiotics by over-producing β-lactamase. See figure 2.4 E.

**(E) By Quorum Sensing (QS):**

Microbes communicate with each other and exchange signalling chemicals (autoinducers) which allows the bacterial population to coordinate gene expression for virulence, conjugation, mobility, apoptosis and antibiotic resistance. This process is termed as "quorum sensing (QS)". A single autoinducer from a single microbe is incapable of inducing any such change but when its colony reaches a critical density (quorum), a threshold of autoinduction is reached and gene expression starts. Several chemically distinct classes of QS-signal molecules have been identified in Gram-negative bacteria. Any drug which can inhibit these signals for virulence or adhesiveness may minimise the risk of microbial growth or resistance to antibiotics.

- **Dangers of Antibiotic Therapy**

Antibiotics are most useful life-saving agents; however they are potentially harmful, if not properly used. The harmful effects are as follows:

- Development of allergic/anaphylactic reactions eg allergic reaction to Penicillin.
- Selective toxicity eg. nephrotoxicity by aminoglycoside antibiotics.
- Development of super-infection eg. resistant staphylococcal entero-colitis.
- Development of multiple- drug-resistant organisms eg MDR/XDR for tuberculosis.
- Deficiency of certain vitamins eg deficiency of vitamin K/folic acid.
- Foetal damage by trans-placental passage eg. some antibiotics are restricted in pregnancy.
- A false sense of security.

**PRINCIPLES OF ANTIBIOTIC DOSING**

Four important characteristics which have a significant influence on the frequency of dosing of an antibiotic are as follows:

- **Minimum Inhibitory Concentration (MIC)**

The MIC is the lowest antibiotic concentration which prevents the growth of microorganism after a 24-hour incubation period with a standard organism inoculation (of $10^4$-$10^5$ cfu/ml). There is another related term Minimum Bacterial Concentration (MBC) which means the lowest concentration of an antibiotic which causes complete destruction of the organism or permits survival of less than 0.1% of the inoculums.

- **Concentration-Dependent Killing Effect (CDKE)**

Some antibiotics are much more effective if higher blood concentrations are reached periodically. The rate and extent of killing action increase with increase in drug concentration. The activity of Aminoglycosides, Fluoroquinolones and Metronidazole are concentration dependent.

- **Time Dependent Killing Effect (TDKE)**

Some antibiotics are more effective if blood levels are maintained above MIC for a longer duration. In case of such antibiotics, the effect is time dependent; hence the effect is termed as time dependent killing effect (TDKE). The length of time above MIC is most important for such drugs. In case of these drugs, the bactericidal activity continues as long as their serum concentrations are above MIC for the entire interval between the doses. The activity of β-lactum antibiotics like Penicillins and Vancomycin are time dependent.

- **Post-Antibiotic Effect (PAE)**

A persistent suppression of bacterial growth after a brief exposure of antibiotic is known as Post- Antibiotic Effect (PAE). In this case, the inhibition of bacterial growth is seen even when the antibiotic is no longer present in bacterial medium or even when its concentration is below MIC. Antibiotics like Aminoglycosides, Fluoroquinolones, Rifampicin, Tetracyclines and Chloramphenicol show significant PAE against most Gram-negative and some Gram-positive organisms.

The antibiotics, on the basis of CDKE, TDKE and PAE can be classified in three groups as follows:

- **Group I: CDKE with prolonged PAE**

Antibiotics from this group kill bacteria more rapidly if their serum concentrations are kept appreciably above MIC. Hence a higher dose with wider dosage intervals can be selected for these drugs. The examples in this category are Aminoglycosides, Fluoroquinolones, Metronidazole analogues and Rifampicin. Gentamycin (aminoglycoside) can be preferably administered in a single dose (7mg/Kg IM, once daily) rather than in a dose of 1.5 mg/Kg, IM, 8 hourly.

- **Group II: TDKE with shorter PAE**

In this group, serum concentrations should be kept above MIC/MBC for as long as possible during dose intervals. The examples are β-lactums, Clindamycin, Macrolides (except Azithromycin) and Clrithromycin. β-lactums with shorter half-life are given at 6 hourly or 8 hourly intervals.

- **Group III: TDKE with prolonged PAE**

In this group, although the duration of antibacterial exposure is important, the clinical effectiveness is not compromised even if their concentration falls below MIC/MBC since they possess longer and persistent PAE besides longer half-life. The examples are Azithromycin and Clarithromycin.

**Antimicrobial Spectrum**

Antibiotics which are active against a single or limited group of pathogens are called to have narrow spectrum eg drugs like INH, Rifampicin are active against Mycobacterium tuberculosis. Antibiotics which are active against wide range of pathogens like Gram-positive, Gram-negative, Spirochaetes, Chlamydia and Rickettsia are called as broad-spectrum antibiotics. A broad-spectrum antibiotic is more likely to cause superinfection or pseudomembranous colitis (PMC) by destroying normal flora of the gut.

**Superinfection**

The organisms present in GIT are termed as normal microbial flora of the individual. Antibiotic therapy markedly reduces this flora allowing invasion by opportunistic organisms like Proteus, resistant staphylococci and Pseudomonas. This is called as superinfection, which is manifested as antibiotic-induced diarrhoea and colitis. Superinfection due to *Clostridium difficile* or *Candida* (fungus) can lead to PMC, which is characterised by bloody diarrhoea, abdominal distension with pain, dehydration and leukocytosis. This is observed with Amoxycillin, third generation Cephalosporins and Clindamycin.

**Classification of Pathogenic Microbes**

- Bacteria
- Spirochaetes
- Rickettsiae
- Chlamydiae
- Miscellaneous

**Classification of Cocci and Bacilli**

- Gram positive cocci
- Gram negative cocci
- Gram positive bacilli
- Gram-negative bacilli
    - Enterobacteriaceae
    - Others

## 2.2 SULPHONAMIDES

Sulphonamides are structural analogues of p-amino benzoic acid (PABA). The structural similarity is shown in Fig. 2.5.

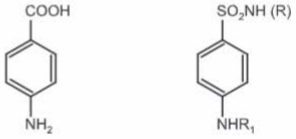



**Fig. 2.5: Structural similarity between PABA and Sulfonamides**

- **Mechanism of Action**

Human cells are freely permeable to exogenously administered folic acid but bacterial cells are not. As a result, the bacteria have to synthesise their own folic acid from PABA. This is necessary for their growth and multiplication. On the contrary, human beings acquire folic acid from the diet. Folic acid is further metabolised in the body. The active form of folic acid is tetrahydrofolic acid (THF) or folinic acid , which is an important coenzyme responsible for synthesis of bacterial proteins from amino acids as well as bacterial RNA and DNA from purines and pyrimidines. Structurally, folic acid consists of three components: a pteridine moiety + PABA + glutamate. Bacterial folic acid synthesis occurs as shown in Fig. 2.6.

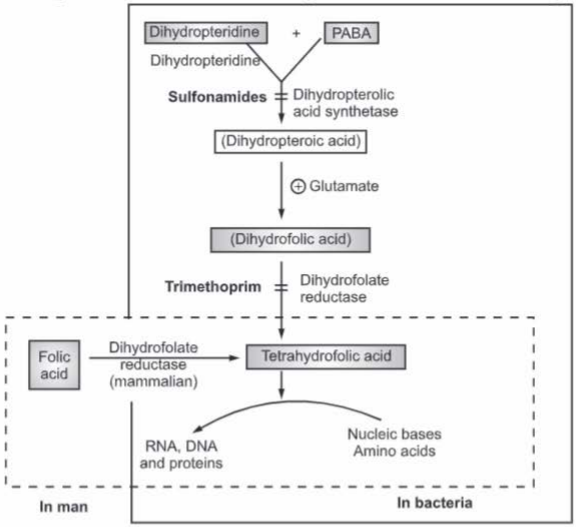



**Fig. 2.6: Bacterial synthesis of folic acid**

Sulphonamides, enter the synthetic sequence in place of PABA by competing for the enzyme dihydropteroic acid synthetase (folic acid synthetase) and thus form a non-functional analogue of folic acid which is of no use to bacteria. Hence it exerts bacteriostatic action. Thus sulphonamides are selectively toxic to bacteria and not to the host cells.

It is implied that antibacterial effects of sulphonamides can be overcome by excess of PABA. Hence a drug which can generate PABA can antagonise action of sulphonamides. Procaine, a local anaesthetic is an ester of PABA and can antagonise actions of sulphonamides. Pus is rich in PABA. In addition, products of tissue breakdown contain thymidine and purines which bacteria can use to bypass the need of folic acid. Thus pus and products of tissue breakdown can antagonise actions of sulphonamides.

- **Classification:**

  Based on clinical utility, sulphonamides can be classified in following three categories:

  - Orally absorbable sulphonamides:

  They are further sub-divided into following three categories:

  (i) Short acting sulphonamides (half-life 6-9 hours): e.g. Sulphacytine, Sulphadiazine, Sulphisoxazole and Sulphamethizole.

  (ii) Intermediate acting sulphonamides (half-life 10-12 hours): eg Sulphamethoxazole and Sulphamoxole.

  (iii) Long acting sulphonamides (half-life 7-8days): eg Sulphadoxine.

  - Orally non-absorbable sulphonamides: eg Sulphasalazine, Olsalazine and Balsalazine.
  - Topical sulphonamides: eg Silver sulphadiazine, Mafenide and Sulphacetamide.

- **Antimicrobial Spectrum**

Sulphonamides are mainly active against Gram-negative bacilli like *E coli, Shigella, Salmonella, Haemophilus influenza, Vibrio cholera* and *Proteus mirabilis* (but not *Pseudomonas aeruginosa, Serratia* or *Proteus* species). Sulphonamides are moderately active against *Neisseria gonorrhoeae* and *N meningitides*. They are also active against actinomycetes like *Nocardia,* rickettsia like *Chlamydia trachomatis* and protozoa like *Toxoplasma gondii.*

- **Resistance**

Gonococci, Staphylococci, Meningococci, Sterptococci, *E coli* and *Shigella* develop reisitance towards sulphonamides. Sulphonamide resistance may occur as a result of mutations that may cause one of the following:

- Over-production of PABA to overpower the inhibition due to sulphonamides or
- Alteration in the nature of dihydro-pteroic acid synthetase enzyme which has a low affinity for sulphonamides or
- Loss of permeability of sulphonamides through bacterial membrane or
- An appearance of an alternative pathway for PABA synthesis.

- **Pharmacokinetics:**

Sulphonamides are well absorbed when given orally, except for those which are designed for local effects on GIT. These are never administered sub-cutaneously or intramuscularly because their solutions are alkaline and injections are painful. Sodium salts of sulphonamides in 5% dextrose can be given intravenously. Topical sulphonamides are absorbed through the skin but the amount of absorbed quantity is very low. A burn area larger than 20% of total body surface can absorb enough drug to cause systemic toxicity, especially if accompanied by renal dysfunction. Sulphonamides are widely distributed and pass through BBB as well as placental barrier. They have good accumulation in prostatic fluid. Longer acting sulphonamides like Sulphamethoxazole and Sulphadoxine are highly protein bound (85-93%). They are metabolised as acetylated conjugates in the liver. Acetylated metabolites are inactive and have low solubility in acidic urine. This leads to precipitation of crystalluria and renal toxicity.

- **Clinical Uses**

Sulphonamides are rarely used as single agents. They are usually used as fixed dose combinations with Trimethoprim or Pyrimethamin. Topical sulphonamides and those for ulcerative colitis are also being used. They are divided into absorbable, non-absorbable and topical sulphonamides.

- **Absorbable Sulphonamides:**

They are used in acute uncomplicated urinary tract infections (UTI) caused by *E coli* and other pathogens, which usually respond to a short acting sulphonamide like Sulphisoxazole.

They can also be used alone as a drug of third choice in conditions like nocardiosis, chancroid due to *Haemophilus ducreyi* and lymphogranuloma due to *Chlamydia*.

- **Non-absorbable sulphonamides**

Sulphisoxazole is widely used in the treatment of ulcerative colitis and in rheumatoid arthritis. It is poorly absorbed through GIT and is degraded by bacterial flora of the colon to 5-amino salicylic acid (5-ASA, Mesalazine) and Sulphapyridine. 5-ASA acts as a anti-inflammatory agent in ulcerative colitis and Sulphapyridine serves as a carrier moiety for 5-ASA. In case of rheumatoid arthritis, Sulphapyridine is the active component.

- **Topical sulphonamides**

Sodium sulphacetamide (10%, 20% or 30%) ophthalmic solutions or ointment is an effective treatment for trachoma due to *Chlamydia trachomatis* and for bacterial conjunctivitis.

Silver sulphadiazine is a relatively less toxic topical sulphonamide ointment and is preferred for prevention of infection in burn cases. It is active against large number of Gram-negative bacteria including *Pseudomonas*. It slowly releases $Ag^+$ which also provides additional anti-microbial action. It is well tolerated; but it may be absorbed from abraded skin to produce systemic toxicity.

Mafenide is a sulphonamide analogue. It is used topically and has activity against Gram-positive and Gram-negative bacteria. It is active even in the presence of pus and effective against *Pseudomonas* and *Clostridia* which are not inhibited by other sulphonamides. It is used in burn cases. It is an inhibitor of the enzyme carbonic anhydrase and may cause irritation at the site of application and also cause acidosis.

- **Adverse effects**

  Following adverse effects are observed with sulphonamides:

  - Crystalluria and renal toxicity.
  - Hypersensitivity reactions.
  - Kernicterus in neonates (a toxic encephalopathy).
  - Haemolytic anaemia (in patients with deficiency of G6PD enzyme).

- **Drug interactions**

Sulphonamides increase the activity of oral anticoagulants, sulphonylurea and methotrexate by displacing them from their protein-binding sites. On the contrary, sulphonamides are displaced from protein-binding site by Aspirin and other NSAIDs.

**Preparations:**

**Absorbable sulphonamides:**

- Sulphadiazine: 500 mg tab (generic): **Sulphadiazine**
- Sulphamoxole: 500 mg tab: **Sulfuno**
- Sulphamethoxazole : 500 mg tab: **Gantanol**

**Topical sulphonamides**

- Sulphacetamide: 10%, 20%, 30% eye drops: **Albucid, Locula**
- Silver sulphadiazine: 1% cream: **Silvirin, Silvindone;** (Silver sulphadiazine 1% + Chlorhexidine 0.2%) cream: **Silverex, Silvindone plus**
- Mafenide: 1% cream: **Sulfamylon**

## 2.3 COTRIMOXAZOLE

There are some synergistic combinations with sulphonamides. They are Cotrimoxazole (generic name) and a combination of Sulphadoxine and Pyrimethamine (for malaria). Cotrimoxazole is discussed below.

It is a combination of Sulphamethoxazole and Trimethoprim in a ratio of 5:1. A Cotrimoxazole tablet contains 400 mg of Sulphamethoxazole and 80 mg of Trimethoprim. A tablet with double strength contains 800 mg and 160 mg of respective drugs. Both the drugs have a half-life of about 11 hours. The combination is bactericidal as compared to bacteriostatic activity of each component. The combination has a wider spectrum of antibacterial activity and delays the development of bacterial resistance. The synergistic

action of this combination results due to blockade of folic acid synthesis at two sites in a sequence. See figure 2.6. The usual oral dose of double strength Cotrimoxazole (DS) tablet is one tablet every 12 hours.

Iclaprim is an analogue of Trimethoprim. When administered intravenously, Iclaprim is more effective and better tolerated than Trimethoprim. It is useful in patients suffering from skin and soft tissue infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA). It is also highly active against Vancomycin-resistant *Staphylococcus aureus* (VRSA), *Sterptococcus pneumonia* and some Gram-negative bacteria.

Cotrimoxazole is active in following indications:

**Urinary Tract Infections (UTIs):** Coliform bacteria including *E coli* and *Proteus mirabilis* respond well to Cotrimoxazole. Acute but uncomplicated cases respond well to 5-10 days of Cotrimoxazole-DS tablets given twice daily.

**Prostatitis:** Cotrimoxazole gets concentrated in prostatic fluid. One DS tablet twice daily for three weeks is effective in acute prostatitis. For chronic infection, the treatment may be continued for 6-12 weeks.

**Respiratory Tract Infections:** Cotrimoxazole is useful for acute sinusitis, bronchitis and otitis media due to *Pneumococcus and Haemophilus* species. One DS tablet twice a day is useful.

**Typhoid:** Cotrimoxazole in a dose of one DS table twice a day for two weeks is used as an alternative to Ciprofloxacin. A 10-12 week course eradicates carrier state of *Salmonella typhi.*

**Bacterial diarrhoeas and dysentery:** Acute gastroenteritis due to *Shigella, Yersinia, Enterocolitica,* traveller's diarrhoea due to *E coli* and cholera due to *Vibrio cholera* respond well to Cotrimoxazole in a adult dose of DS tablet twice daily for 7 days. Ciprofloxacin or Norfloxacin are the drugs of choice for this indication.

**Nocardiosis:** Cotrimoxazole is the drug of choice for pulmonary lesions or brain abscess due to *Nocardia.*

**Sexually Transmitted Diseases (STDs):** Cotrimoxazole-DS tablet twice a day for 7 days is the drug of choice for chancroid due to *Haemophilus ducreyi.* Non-specific urethritis, lymphogranuloma due to *Chlamydia* and gonorrhoea due to *Neisseria gonorrheae* respond to Cotrimoxazole.

**Pneumonia:** Cotrimoxazole is drug of choice for treating pneumonia due to *Pneymocystitis carinii* in neutropenic and AIDS patients. The drug is used as DS one tablet four times a day for 2-3 weeks as a curative. Alternatively, one DS tablet once a day is used prophylactically.

**Melioidosis:** Cotrimoxazole or a combination of Sulphadiazine, Sulphamerazine and Sulphamethazine can be used for treating meliodosis caused by *Burkholderia pesudomaller.*

Intravenous Cotrimoxazole, in 5% dextrose solution is preferred to treat moderate/severe pneumonia, shigellosis, typhoid fever, nocardiasis and Gram-negative bacterial sepsis. An IV solution usually contains 80 mg of Trimethoprim and 400 mg of Sulphamethoxazole per 5 ml further diluted in 125 ml of 5% dextrose solution. It is then administered by IV infusion over a period of 60-90 minutes.

**Preparations:**

- (Sulphamethoxazole 400 mg + Trimethoprim 80 mg) tab, (Sulphamethoxazole 200 mg + Trimethoprim 40 mg)/ 5 ml suspension: **Bactrim, Ciplin, Septran;** (Sulphamethoxazole 800 mg + Trimethoprim 160 mg) tab: **Bactrim DS, Ciplin DS, Septran DS;** (Sulphamethoxazole 400 mg + Trimethoprim 80 mg)/ 5 ml injection: **Oriprim-IV**
- (Sulphamoxole 400 mg + Trimethoprim 80 mg) tab, (Sulphamoxole 200 mg + Trimethoprim 40 mg)/ 5 ml suspension: **Supristol;** (Sulphamoxole 800 mg + Trimethoprim 160 mg) tab: **Supristol DS**

## 2.4 ANTIBIOTICS

### 2.4.1 Penicillins

The first antibiotic to enter in clinical practice was Penicillin. It belongs to the group of β-lactam antibiotics. This group consists of four subtypes: Penicillins, Cephalosporins, Monobactams and Carbapenems. The first two types are discussed here.

Penicillin was originally obtained from the fungus *Penicillium notatum*. However, commercially used high- yielding variety is *Penicillium chrysogenum*. Penicillins have following important features:

- All penicillins consist of a sulphur-containing thiazolidine ring (A), fused with a β-lactam ring (B) to which a side chain is attached at position 6 (-NHCOR). See Fig. 2.7.
- The active moiety of penicillin structure is 6-amino penicillanic acid (6-APA) which consists of an intact β-lactam ring (B), having a $-NH_2$ group at position 6, joined to a thiazolidine ring (A). See Fig. 2.7.
- Large quantities of 6-APA are produced from cultures of *Penicillium chrysogenum*. Various side chains (R) are linked to 6-APA. This leads to formation of various synthetic penicillins. Benzyl penicillin (R = benzyl) is one example.
- Most of the penicillins are available as their sodium/potassium salts to carboxyl group of penicillin.
- Some amine salts like procaine penicillin G and benzathine penicillin G are available as sustained release depot injections.

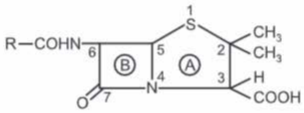



**Fig. 2.7: Prototype structure of penicillins**

- The β-lactam ring of penicillins can be degraded by β-lactamase enzyme produced by invading bacteria. The β-lactam ring can also be hydrolysed by gastric acid. The resultant product viz penicilloic acid is devoid of any antibacterial activity. However, it can combine with proteins from the host leading to formation of an antigen. Penicillin-induced hypersensitivity is caused by these antigens. See Fig. 2.8.

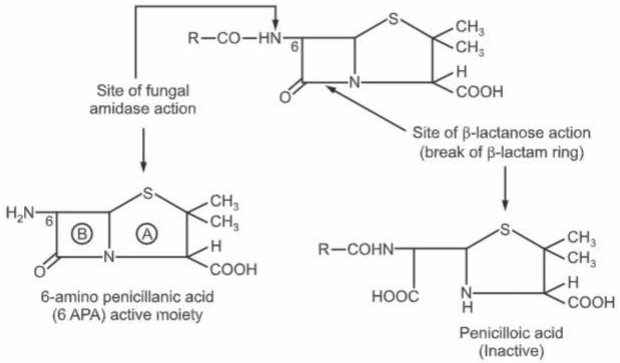



**Fig. 2.8: Degradation of penicillins**

**Mechanism of Action**

Bacteria have no mechanism to regulate osmolarity. They have to utilise a supportive structure around the cell to withstand osmotic changes due to inherent high and low external osmotic pressure of the environment. As a result, majority of bacteria are surrounded by a thick wall which confers stability and rigidity to their structure. Their cell wall is composed of peptidoglycan, which is composed of glycan (a polysaccharide) chain cross linked by peptide chains. See Fig. 2.9. This peptidoglycan layer envelopes the cell and does not allow bacteria to swell and prevents its death due to lysis.

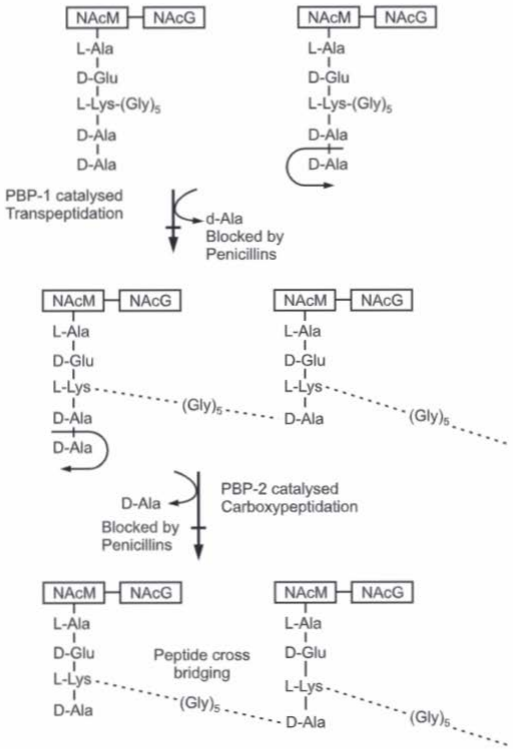


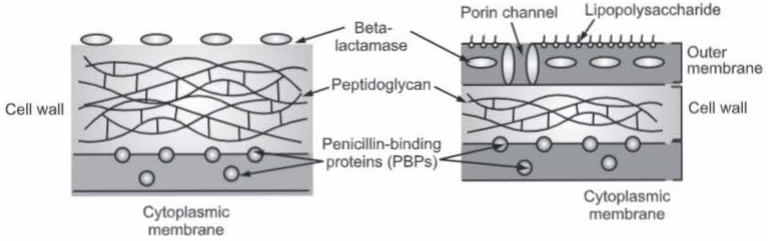

**Fig. 2.9: Biosynthesis of penicillins**

The glycan chain consists of repeating units of two amino sugars: N-acetylmuramic acid (NAcM) and N-acetylglucosamine (NAcG). The pentapeptide side chain with amino acid sequence shown in Fig. 2.9 is linked to NAcM. These peptide chains are cross linked to other peptide chains by a pentaglycine bridge which extends from L-lysine residue of one peptide to the D-alanine residue of another peptide chain. See Fig. 2.9. This cross bridging between the peptidoglycan strands provides necessary strength to the bacterial cell wall. This process is catalysed by penicillin-binding-proteins (PBPs) located on trans-membrane surface enzymes present in bacteria.

Penicillins compete and inhibit PBPs. The formation of an imperfect cell wall leads to osmotic drive of fluid outside to inside leading to death of bacteria. Since rapid cell wall

synthesis takes place when bacteria are multiplying, penicillins are lethal in multiplying phase rather than dormant phase.

The bactericidal activity of penicillins is greater against Gram –positive than Gram-negative bacteria. As shown in Fig. 2.10. Gram-positive bacteria have a thicker layer of peptidoglycan and teichoic acid (a polylol phosphate polymer surrounding the cell membrane). Their peptidoglycan layer is easily accessible to β-lactam antibiotics. On the contrary, Gram-negative organisms have two membranes, the cytoplasmic membrane and an outer membrane with a thin layer of peptidoglycan sandwiched between the two. See Fig. 2.10. The outer membrane consists of lipopolysaccharides with narrow porin channels which functions as barriers to permeability of β-lactam antibiotics and hence weaker activity.




**(a) Gram positive organism** **(b) Gram negative organism**

**Fig. 2.10: Structure of cell walls**

**Classification and Antimicrobial Spectrum**

Penicillins are classified according to their antimicrobial spectrum. Within each of these groups, they are sub-classified as narrow spectrum and extended spectrum Penicillins. Both the groups are further sub-divided into acid stable and acid labile category. See Tables 2.1 and 2.2 for further details.

**Table 2.1 : Classification of narrow spectrum Penicillins.**

| **β-lactamase sensitive (natural)** | | **β-lactamase resistant (anti-staphylococcal)** | |
|---|---|---|---|
| **Acid stable** | **Acid labile** | **Acid stable** | **Acid labile** |
| Penicillin V (phenoxymethyl penicillin) (oral) | Penicillin G (benzyl penicillin), (IM, IV) | Cloxacillin (oral, IM) | Methicillin (IM, IV) |
| – | Procaine penicillin-G (IM depot inj) | Dicloxacillin (oral, IM) | Nafcillin (IM, IV) |
| – | Benzathine penicillin G (IM depot inj) | Flucloxacillin (oral, IM) | – |

**Table 2.2 : Classification of extended spectrum Penicillins: All are sensitive to β-lactamase.**

| Acid stable (amino penicillins) | Acid labile (anti-pseudomonal penicillins) |
|---|---|
| Ampicillin (oral/parenteral) | Carbenicillin (parenteral) |
| Bacampicillin (oral/parenteral) | Ticarcillin (parenteral) |
| Talampicillin (oral/parenteral) | Piperacillin (parenteral) |
| Amoxicillin (oral/parenteral) | Mezlocillin (parenteral) |
| | Aziocillin (parenteral) |

**Narrow Spectrum Penicillins (See Table 2.1)**

Penicillin- V and Penicillin-G are natural penicillins. Both are β-lactamase sensitive, but Penicillin-V is acid stable and can be given orally. On the contrary, Penicillin-G is acid labile and has to be given by IM or IV route. Procaine penicillin-G and Benzathine penicillin-G are depot intramuscular preparations of Penicillin-G.

**Pharmacokinetics (See Table 2.2)**

They have a delayed but sustained absorption leading to prolonged half-life. After distribution in body, Penicillin-G concentrations in most tissues are equal to those in serum except in eye, prostate and CNS where the penetration is poor.

Penicillin-G is excreted by the kidneys. Its 90% elimination occurs via tubular secretion and 10% through glomerular filtration. Probenecid blocks tubular secretion of Penicillin. Methicillin and Nafcillin are acid labile and can be given by IM or IV route. Cloxacillin and Dicloxacillin are acid stable and can be given orally. Their absorption is impaired by food. Nafcillin is cleared by biliary excretion while Cloxacillin and Dicloxacillin are eliminated by both renal and biliary route. Flucloxacillin is similar to Dicloxacillin.

**Anti-microbial Spectrum and Uses:**

For this purpose, narrow spectrum Penicillins have been sub-grouped under β-lactamase sensitive and β-lactamase resistant types. They are discussed below:

**Narrow spectrum, β-lactamase sensitive group:**

The examples in this category are Penicillin-V and Penicillin-G. They are highly effective against Gram-positive cocci and bacilli; equally effective against spirochaetes; moderately active against Gram-negative bacilli and bacteroids.

- Gram-positive cocci: Natural Penicillins are highly active against *Staphylococcus pyogenes* (pharyngitis, otitis media); *Streptococcus pneumonia* (pneumonia); *Streptococcus viridians* and *S faecalis* i.e. *Enterococcus* (sub-acute bacterial endocarditis, SABE). Combination with aminoglycoside antibiotic like Gentamycin works well to treat enterococcal endocarditis. They are also effective against β-*haemolytic Streptococci* and are useful to treat streptococcal pharyngitis (rheumatic fever).

- Gram –positive bacilli: Penicillin-G is the drug of choice for treating infections of *Clostridium tetani* (tetanus); *Clostridium perfringens* (gas gangrene); *Corynebacterium diptheriae* (diptheria); *Bacillus anthracis* (anthrax) and *Listeria monocytogenes* (meningitis, Listeriosis). For diphtheria, tetanus and gas gangrene, anti-toxins are available and are more useful. Penicillin-G has adjuvant role. Spirochetes like *Treponema pallidum* (syphilis) are sensitive to Penicillins. Penicillin-G is moderately active against *Neisseria meningitides* (meningitis) and *Niesseria gonorrhoea* (gonorrhoea). It is effective against actinomycetes like *Actinomyces israelli* (cranio-facial/thoracic/abdominal abscess).

**Narrow Spectrum, β-lactamase Resistant Group:**

The examples in this category are: Cloxacillin, Dicloxacillin, Methicillin and Nafcillin. Their antimicrobial spectrum is similar to that of Penicillin-G; but they are additionally effective against β-lactamase producing *Staphylococci;* hence called as anti-staphylococcal Penicillins. Methicillin-resistant organisms have been labelled as MRSA. Nafcillin is preferred for parenteral use. Cloxacillin and Dicloxacillin are orally active. These are used to treat infections like osteomyelitis, septicaemia, endocarditis and cellulitis caused by susceptible strains of staphylococci. In addition, Cloxacillin can also be used to treat mild staphylococcal skin infection like impetigo.

**Extended Spectrum Penicillins:**

All these Penicillins are β-lactamase sensitive, but aminopenicillins like Ampicillin and Amoxycillin are acid stable. They can be given orally. Carboxypenicillins like Carbenicillin and Ticarcillin as well as ureidopenicillins like Piperacillin, Mezlocillin and Azlocillin are acid- labile and are given by IV or IM route. See Table 2.2.

**Pharmacokinetics:** The pharmacokinetics of Ampicillin and Amoxycillin are similar. Both have adequate bioavailability. Ingestion of food decreases bioavailability of Ampicillin but not of Amoxycillin. Hence Ampicillin should be administered one hour before or after meals. Ampicillin achieves therapeutic concentrations in CSF during inflammatory conditions but Amoxycillin does not. Hence Amoxycillin is not suitable for treating meningitis. The primary route of excretion is kidney. Bacampicillin and Talampicillin are pro-drugs of Ampicillin. Bacampicillin, Talampicillin and Amoxycillin disturb the intestinal flora to a lesser extent; hence incidence of diarrhoea is less.

Carbenicillin, Ticarcillin, Piperacillin, Mezlocillin and Azlocillin are parenteral Penicillins available as sodium salts; they should be administered with caution in patients of CHF. They have very low concentration in CSF. All undergo renal elimination and need dose adjustment in renal failure. Carbenicillin is also available as Indanyl sodium salt. This formulation is acid stable and can be given orally. Mezlocillin has significant hepatic metabolism and requires adjustment of dose in patients with hepatic failure.

**Antimicrobial spectrum and uses :** Aminopenicillins (Ampicillin and Amoxycillin) have hydrophilic character; hence they have enhanced ability to penetrate through porin channels of Gram-negative bacteria. See figure 2.10 (B). hence they have an extended spectrum against some Gram-negative bacteria except for *Pseudomonas aeruginosa*.

Gram-negative bacilli which are killed by aminopenicillins are: *Bordetella pertusis* (whooping cough), *Haemophilus influenza* (pneumonia, otitis media, sinusitis), *E coli, Proteus mirabilis* (UTI), *Salmonella typh,*(typhoid), *Shigella* (diarrhoea). They are not active against *Pseudomonas, Klebsiella, Serratia, Citrobacter,* indole-positive *Proteus* and other Gram-negative aerobes. Presently, Fluoroquinolones have replaced Ampicillin for treating UTI and Amoxycillin for treating typhoid and dysentery. Amoxicillin is used for eradication of *Helicobacter pylori* in treating gastric and duodenal ulcer.

Ampicillin and Amoxycillin are effective against *Sterptococcus viridians*, enterococci and pneumococci. Only Ampicillin is effective in meningitis caused by *Listeria monocytogenes*.

Amongst carboxypenicillins (Carbenicillin and Ticarcillin) Carbenicillin has become obsolete and is replaced by Ticarcillin. It is active against *Pseudomonas aeruginosa* and indole-positive *Proteus* which are not inhibited by aminopenicillins. Hence they are called as anti-pseudomonal penicillins.

Ureiodopenicillins (Piperacillin, Mezlocillin and Azlocillin) have similar chemical outcome like Ticarcillin for *Pseudomonas* infection. In addition, they are also active against *Klebsiella pneumonia* and *Enterobacter*. For treating serious infections due to *Pseudomonas, Proteus or Klebsiella* in case of burns, septicaemia, UTI and in immunocompromised patients, a combination of Piperacillin and Gentamycin is preferred.

The activity of natural Penicillins is measured in terms of units. Crystalline sodium Penicillin-G contains 1600 units/mg. Thus, 1 unit of Penicillin-G = 0.625 µg; or 625 mg of Penicillin-G = 1 million units. Semi-synthetic Penicillins are prescribed on weight basis rather than units.

**Resistance to Penicillin:**

Bacterial resistance to Penicillin may arise from one of the following mechanisms:

- Inactivation of β-lactam ring by β-lactamase.
- Modification of Penicillin Binding Proteins (PBPs).
- Reduction of Penicillin permeability to reach PBPs.
- Activation of antibiotic efflux mechanisms.

**β-lactamase Inhibitors:**

The examples in this category are: Clavulanic acid (derived from *Streptomyces clavligerus*), Sulbactam (semi-synthetic) and Tazobactam (analogue of Sulbactam). They bind irreversibly to the catalytic site of susceptible β-lactamases, produced by bacteria, to prevent hydrolysis of Penicillins. They can inhibit plasmid-mediated β-lactamases which are responsible for transferred drug resistance, such as those produced by Methicillin-sensitive *Staphylococcus aureus, H influenza, H ducreyi, E coli, K pneumonae, P mirabilis, N gonorrhoea, Salmonella and Shigella*. They are unable to inhibit chromosomally mediated β-lactamases found in *Enterobacter, P aeruginosa, Citrobacter and Serratia*.

Only Clavulanic acid is orally absorbed. Others are given by IV or IM. Fixed dose combinations are available in the form: Clavulanic acid + Amoxycillin; Sulbactam + Ampicillin; Tazobactam + Piperacillin.

Addition of Clavulanic acid with Amoxycillin extends the antimicrobial spectrum against β-lactamase producing bacteria, eg *Streptococcus pneumoniae, H influenza and Moraxella*( otitis media, sinusitis and respiratory tract infections), Methicillin-sensitive *S aureus* (MSSA), *K pneumonia* (nosochomial pneumonia), *N gonorrhoae* (gonorrhoea), anaerobes (intra-abdominal abscess), *E coli, Proteus and Klebsiella* (UTI). All β-lactamase inhibitor combinations require dose adjustments in patients with renal insufficiency because they are excreted by kidney. Adverse effects are GI intolerance, stomatitis and rashes.

**Adverse Effects:**

**(1) Hypersensitivity reactions:** 5-8% patients receiving Penicillin experience hypersensitivity reactions. The major antigenic determinant is penicilloic acid, but minor determinants like benzyl penicillin or sodiumbenzylpenicilloate can also combine with host proteins to become antigenic. Allergic reactions are classified into three sub-categories as mentioned below:

**(i) Immediate hypersensitivity reactions:** These occur within 20 minutes of parenteral administration of penicillins. They are mediated by IgE antibodies. Manifestations include urticaria, pruritus, wheezing, sneezing and rhinitis. In few cases (0.05%), it may manifest as diffused pruritus, hypotensive shock, angioneurotic oedema, choking, loss of consciousness and death. Management includes administration of adrenaline (SC/IM), corticosteroids (IV/IM), antihistamine (IM) with supportive measures like oxygen inhalation, IV fluids and plasma expanders.

**(ii) Accelerated hypersensitivity reactions:** These occur within 72 hours of penicillin administration, and are mediated by IgE antibodies against major antigenic determinant. Manifestations include rash, fever and urticaria and rarely angioneurotic oedema. It is less likely to be fatal.

**(iii) Late hypersensitivity reactions:** These occur after 72 hours of administration. They are mediated by IgE and IgM antibodies against major antigenic determinants. Manifestations include morbiliform, urticarial or erythematosus eruptions, local inflammatory reactions, lymphadenopathy, spleenomegaly, serum sickness and Coombs positive haemolytic anaemia.

**(2) GIT side effects:** Diarrhoea is more common with Ampicillin than Amoxycillin, Bacampicillin or Talampicillin. Glossitis, stomatitis and abnormal taste sensation may occur after oral use.

**(3) Miscellaneous effects:** Oxacillin can cause reversible elevations of SGOT and SGPT. Methicillin can cause interstitial nephritis. High doses of Carbenicillin/ Ticarcillin may produce reversible increase in prothrombin time leading to bleeding problem. High dose of Carbenicillin can be neurotoxic. Penicillin, injected in syphilitic patients may cause Jarisch-Herxheimer reaction, characterised by shivering, fever, myalgia and collapse due to sudden release of spirochaetal breakdown products.

**Drug Interactions:**

They are of two types: antagonistic and synergistic.

**Antagonistic combinations:**

- Oral penicillins (Penicillin V, Ampicillin) may be antagonised by antibiotics like Tetracyclines, Chloramphenicol, Erythromycin; because they diminish bactericidal effect of Penicillins by inhibiting bacterial growth.
- Penicillins and Aminoglycosides (eg Gentamycin) should not be mixed in the same syringe; because they inactivate each other. They should be injected separately.
- Ampicillin with Allopurinol may cause non-urticarial maculopapular rash.
- Hydrocortisone inactivates Ampicillin if mixed in IV fluid.

**Synergistic combinations:**

- Probenecid prolongs the action of Penicillins by decreasing its tubular secretion.
- β-lactamase inhibitors extend the spectrum of penicillins against β-lactamase producing cocci and bacilli.
- Procaine penicillin-G with Gentamycin is a synergistic combination against *Sterptococcus viridians* and *Sterptococcus faecalis.*
- Piperacillin and Gentamycin are synergistic against *Pseudomonas and Proteus.*
- A fixed dose combination of Ampicillin/Amoxycillin (250 mg) with Cloxacillin (250 mg) is synergistic in post-operative and respiratory infections; however, this combination is irrational because sub-therapeutic doses increase chances of resistance.

**Preparations**

**Narrow Spectrum Penicillins:**

- Sodium Penicillin-G: 0.5 MU, 1 MU injection: **Benzylpen**
- Procaine Penicillin-G: 0.5 MU, 1MU dry powder for IM injection: **Procaine Penicillin-G (PPG)**
- Fortified Procaine Penicillin-G: (Procaine Penicillin 3 lac U + Sod Penicillin-G 1 lac U) injection: **FPP**
- Benzathine Penicillin-G:0.6 MU, 1.2 MU, 2.4 MU injection: **Pencom, Penidure-LA**
- Penicillin-G Potassium: 0.2 MU, 0.4 MU, 0.8 MU tab: **Pentids**
- Penicillin-V: 125 mg, 250 mg tab; 125 mg/5 ml dry syrup: **Crystapen-V**
- Cloxacillin: 250 mg, 500 mg/vial injection: **Bioclox, Neoclox;** 250 mg, 500 mg injection; 250 mg, 500 mg cap, 125 mg/3 ml suspension: **Klox**
- Dicloxacillin: 250 mg, 500 mg cap: **Klox-D**
- Flucloxacillin : 250 mg cap, 250 mg/vial injection: **Neoflox**

**Extended Spectrum Penicillins**

- Amoxicillin: 250 mg, 500 mg cap, 125 mg/5ml dry syrup: **Mox, Novamox, Genmox, Moxibact;** (Amoxycillin 250 mg + Cloxacillin 250 mg): **Novaclox;** (Amoxycillin 500 mg + Probenecid 500 mg) tab: **Moxylong;** (Amoxycillin 250 mg + Clavulanic acid 125 mg) tab, (Amoxycillin 1 gm + Clavulanic acid 200 mg)/vial injection, (Amoxycillin 125 mg + Clavulanic acid 31.25 mg)/5 ml dry syrup: **Augmentin, Enhancin, Nuclav, Duo, Symbiotik-XL**
- Ampicillin: 250 mg, 500 mg cap, 125 mg/5 ml dry syrup, 250 mg, 500 mg/vial injection: **Albercilin, Roscillin, Ampilin;** (Ampicillin 500 mg + Probenecid 500 mg) tab: **Ampilong;** (Ampicillin 250 mg + Cloxacillin 250 mg) cap and per vial injection: **Duoclox, Megapen, Roscilox;** (Ampicillin 1 gm + Sulbactam 500 mg) per vial injection: **Sulbacin, Betaamp, Ampitum**
- Bacampicillin: 200 mg, 400 mg tab: **Penglobe**
- Carbenicillin: 1 gm, 5 gm/vial injection: **Carbelin**
- Piperacillin : 2 gm, 4 gm/vial injection: **Pipracil;** 1 gm, 2 gm/vial injection: **Piprapen;** (Piperacillin 4 gm + Tazobactam 500 mg)/vial injection: **Pybactum, Tazact, Zosyn;** (Piperacillin 2 gm + Tazobactam 250 mg)/vial injection: **Microtaz, Tazar, Tazact**

## 2.4.2 Cephalosporins

The general structure of Cephalosporins is shown in Fig. 2.11. Structurally they are similar to Penicillins with the difference that ring A in Cephalosporin is a six membered ring while in Penicillins it is a five membered ring. The six membered ring of Cephalosporins is that of dihydrothiazine, fused with a β-lactam ring. The active nucleus of Cephalosporins is obtained from *Cephalosporinium acremonium*. Most of the derivatives are semisynthetic with chemical modifications at position 3 and 7.

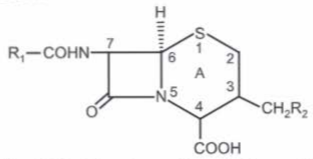



**Fig. 2.11: Structure of Cephalosporin**

Cephalosporins are similar to Penicillins in mechanism of action and adverse effects. Except for the first generation drugs, rest are resistant to β-lactamase (cephalosporinase). All Cephalosporins have a broad spectrum of activity against Gram-negative bacteria and anaerobes as compared to Penicillins. However, no Cephalosporin is active against *Enterococcus faecalis*, MRSA and Gram-positive bacteria.

**Mechanism of Action:**

Just like Penicillins, Cephalosporins inhibit transpeptidation process leading to formation of imperfect cell wall. Osmotic drive from external environment of the host cell causes

activation of autolysin enzyme leading to lysis of bacteria. Cephalosporins are bactericidal drugs.

**Classification:**

Cephalosporins are classified into different generation products. First generation were introduced in 1960s followed by second generation in 1970s, third generation 1980s, fourth generation in 1997 and fifth generation in around 2010.

**(1) First Generation Cephalosporins:**

The examples in this category are: Cephalexin (oral), Cefadroxil (oral), Cephradine (oral/parenteral) and Cefazolin (parenteral).

Oral Cephalosporins are generally well absorbed. They do not cross BBB; hence they are not suitable for trearting brain abscess or meningitis. Metabolism is not a major elimination path. They are excreted through kidney. Probenecid increases plasma concentration and prolongs half-life by inhibiting their renal tubular secretion. Except for Cefadroxil, which is given 12 hourly, all others are administered on 6-8 hourly basis. All are sensitive to degradation by β-lactamase.

Cephalosporins have notable activity against Gram-positive cocci like streptococci, pneumococci and methicillin-sensitive staphylococci. However they do not inhibit MRSA and *Enterococcus faecalis*. They show moderate activity against Gram-negative bacteria like *E coli, K pneumonia, and* indole- negative *P mirabilis*. They are not active against *Pseudomonas, Salmonella, Enterobacter,* indole-positive *Proteus, Serratia and Acinetobacter*. They have insignificant activity against Gram-positive bacilli. While they are active against anaerobic Gram-positive cocci like peptococci, they are inactive against anaerobic Gram-negative bacteria like B*acteroids fragilis*.

First generation Cephalosporins are used for treatment of UTIs, minor staphylococcal infections or for infections like cellulitis or soft tissue abscess. They are ineffective in meningitis. Cephazolin has relatively better penetration in tissues; hence it is the drug of choice in surgical prophylaxis before cardiac surgery and orthopaedic, prosthesis procedures.

**(2) Second Generation Cephalosporins:**

The examples in this category are Cefaclor (oral), Cefuroxime (oral or parenteral), Cefprozil (oral), Cefotetan (parenteral), Cefamandole (parenteral) and Cefoxitin (parenteral).

Cefaclor, Cefuroxime axetil and Cefprozil are orally active with good bioavailability. Cefuroxime axetil is a pro-drug which is hydrolysed by enzymes in intestinal mucosa. Only Cefuroxime crosses BBB. Except for Cefaclor, these drugs are more stable to β-lactamase degradation. The intra-muscular injections are painful; hence intravenous route is preferred. They are excreted unchanged through kidney. Probenecid, by competing at tubular secretion increases half-life and plasma concentration.

All second generation Cephalosporins are less active against Gram-positive cocci and bacilli as compared to first generation drugs. They have an extended action on Gram-negative organisms including some anaerobes. Cefoxitin and Cefotetan have good anaerobe activity and are useful in treating peritonitis, diverticulitis and some gynaecological infections.

Cefaclor and Cefprozil are more active than first generation drugs against *H influenza, M catarrhalis, E coli and P mirabilis*. They are primarily used for treating upper respiratory infections. Cefuroxime is resistant to β-lactamase producing Gram-negative bacteria like penicillinase- producing *N gonorrhoae, H influenza and K pneumonia*; hence it is used to treat community-acquired pneumonia. It is also used to treat meningitis. It is active against Gram-positive cocci like *S pneumoniae, and S pyogenes*, but not against *S aureus*. Cefamandole is similar to Cefuroxime and is preferred to treat STDs. The use of second generation Cephalosporins has declined for two reasons: 1) Penicillin + β-lactamase inhibitor combination is better alternative against *B fragilis* and 2). For infections of Gram-negative organisms third and fourth generation drugs are preferred.

**(3) Third Generation Cephalosporins:**

The examples in this category are: Cefixime (oral), Cefpodoxime (oral), Ceftibuten (oral), Cefdinir (oral), Cefditoren (oral), Cefoperazone (parenteral), Ceftriaxone (parenteral), Cefotaxime (parenteral), Ceftazidime (parenteral) and Ceftrizoxime (parenteral).

All these drugs provide adequate therapeutic levels in CSF. Ceftriaxone has relatively long plasma half-life (7-8 hours) and high protein binding (90%); hence it is administered once daily. Cefotaxime is metabolised to an active metabolite, desacetyl cefotaxime. Cefoperazone and Ceftriaxone are excreted through bile and do not need any dose adjustment in renal insufficiency. Urinary excretion is the major elimination route for other Cephalosporins and need dosage adjustment in renal insufficiency. Probenecid can increase plasma concentration of Cephalosporins. All these drugs are highly resistant to degradation by β-lactamases produced by Gram-negative bacteria.

These drugs are highly active against Gram-negative cocci, Gram-negative bacilli and anaerobes. They have an excellent activity against *N gonorrhoae, N meningitides, E coli, Enterobacter, H influenza, K pneumonia and P mirabilis*. Cefoperazone and Ceftazidime are active against *P aeruginosa*. These drugs are a drug of choice for serious infections caused by *Klebsiella, Enterobacter, Proteus, Serratia and Haemophilus species*. They are less active than first generation drugs against Gram-positive cocci.

**Ceftriaxone** is effective in treating meningitis. A single intramuscular dose of 200 mg is effective in treatment of gonorrhoea and chancroid. It is excellent for community- acquired pneumonia caused by pneumococci, *H influenza and S aureus*. It is also effective in treating complicated UTIs, abdominal sepsis and septicaemias. It can be used to treat multi-drug resistant typhoid fever in relative high doses of 4 gm intravenous daily for 2 days followed by 2 gm intravenous per day till 2 days after fever subsides.

**Cefotaxime** is useful for treating meningitis and community acquired pneumonia. A single dose of 0.5-1 gm given intramuscularly, is effective in treating gonorrhoea. It has been used in respiratory, genito-urinary/abdominal infections, septicaemia, anaerobic and hospital-acquired infections.

**Cefoperazone** is more active than Cefotaxime against *Pseudomonas;* but less active than Ceftazidime. It is active against *S typhi and B fragilis*. It is used for pseudomonal UTIs,

bacteraemia and infections in immunocomprised patients. It is also useful in meningitis, gonorrhoea and septaemia.

**Ceftazidime** is good against pseudomonas (better than Cefoperazone) and other Gram-negative bacilli. Ceftazidime in association with Aminoglycosides is a drug of choice for pseudomonal meningitis. It is useful for nosochomical infections also.

**Ceftrizoxime** is similar to Cefotaxime except for higher activity against *B fragilis*.

**Cefixime and Cefpodoxime** are orally active in a dose of 200-400 mg BD. Cefixime is used to treat respiratory, urinary and biliary infections. A single 400 mg oral dose is enough for uncomplicated gonorrhoea. It is not active against *S aureus, Pseudomonas*. Cefpodoxime is similar to Cefixime but is active against *S aureus*. Its usual dose is 200 mg BD.

**Ceftibuten, Cefdinir and Cefditoren pivoxil** are orally active against both Gram-positive and Gram -negative bacteria. They are used to treat community acquired pneumonia, chronic bronchitis, otitis media, sinusitis, pharyngitis, tonsillitis and skin infections. Cefdinir is given in a dose of 300 mg BD; Ceftibuten as 400 mg once daily and Cefditoren pivoxil in a dose of 400 mg BD.

In neutropenic, febrile immunocompromised patients, third generation Cephalosporins are often used with Aminoglycosides. The combination may have higher nephrotoxicity and should be used with caution.

**(4) Fourth Generation Cephalosporins:**

The examples in this category are Cefpirome (parenteral), Cefepime (parenteral) and Cefozopran (parenteral).

Cefepime is given by intramuscular/intravenous injection in a dose of 1-2 gm 8 hourly. Its plasma half-life is 2 hours. It is widely distributed in body tissues and fluids and accumulates in CSF. It is eliminated to the extent of 85-90% through kidney. Other two drugs are less commonly used.

They are resistant to degradation by several forms of β-lactamases. They are active against Gram-positive cocci like methicillin-sensitive *S aureus, S pneumonia*. Their activity is similar to that of third generation Cephalosporins but they are highly active against Gram-negative organisms like *P aeruginosa, Enterobacteriacae, Haemophilus, Proteus and Neisseria.* They are also active against bacteria which were resistant to earlier group of Cephalosporins. They are used against hospital-acquired pneumonia, bacteraemia and septicaemia. They are also active against UTIs, respiratory tract infections and for febrile neutropenic patients.

**(5) Fifth Generation Cephalosporins:**

The examples in this category are Ceftobiprole and Ceftaroline (both parenteral).

They have slightly different unique mechanism of action. They effectively bind to and inhibit penicillin-binding protein-2a (PBP-2a) produced by MRSA and penicillin-resistant *S pneumonia,* which is not inhibited by majority of antibiotics in clinical use.

There is notable increase in their activity against Gram-positive cocci (MRSA, Penicillin-resistant *S pneumonia and Enterococcus*). In addition, they retain the activity of fourth

generation Cephalosporins against Gram-negative bacilli like *E coli and Pseudomonas*. They have limited activity against anaerobes.

**Ceftaroline** is used for treatment of community-acquired bacterial pneumonia and acute bacterial skin infections including MRSA. **Ceftobiprole** exhibits post-antibiotic effect against MRSA and *S pneumonia*. Both are excreted by kidney. There is a need of dose adjustment in renally compromised patients. None of them inhibit CYP450 isoenzymes.

**Adverse Effects:**

- Hypersensitivity reactions.
- Superinfection, pseudomembranous colitis (PMC) and diarrhea.
- Coagulation abnormalities.
- Pseudolithiasis (only with Ceftriaxone).
- Local irritation and pain after intramuscular injection.

**Drug Interactions:**

- Antacids decrease absorption of Cefaclor, Cefdinir and Cefpodoxime.
- Food decreases oral absorption of Cefuroxime and Cefpodoxime.
- Cefoperazone, Cefotetan and Cefamandole can induce disulfiram-type reaction against alcohol due to inhibition of aldehyde dehydrogenase.
- Probenecid enhances plasma levels and duration of action of those Cephalosporins which are excreted through renal tubule.
- Aminoglycosides should not be mixed in the same syringe with Cephalosporins.
- Combinations of Cephalosporins with Salbactam and Clavulanic acid have an extended spectrum against β-lactamase producing bacteria.

**Preparations**

**First Generation Cephalosporins:**

- Cefazolin: 250 mg, 500 mg, 1 gm/vial injection: **Cezolin, Orizolin, Reflin.**
- Cephalexin: 250 mg, 500 mg cap, 100 mg/ml drops, 125 mg, 250 mg DT-tab: **Sporidex, Phexin, Ceff.**
- Cefadroxil: 500 mg tab, 250 mg/5ml suspension/dry syrup, 125 mg paed tab/DT tab: **Cefadrox, Droxyl, Odoxil.**
- Cephradine : 250 mg, 500 mg, 1 gm/vial injection: **Ceflad.**

**Second Generation Cephalosporins:**

- Cefaclor: 250 mg cap, 125 mg, 250 mg D tab, 125 mg/5 ml dry syrup: **Keflor, Vercef, Distaclor.**
- Cefuroxime axetil: 125 mg, 250 mg tab: **Altacef, Pulmocef, Ceftum;** 250 mg, 750 mg, 1.5 gm/vial injection: **Supacef, Altacef, Spizef.**
- Cefprozil : 250 mg, 500 mg tab: **Orprozil.**

**Third Generation Cephalosporins:**

- Cefixime: 100 mg, 200 mg tab, 50 mg/5ml dry syrup: **Topcef, Cefix, Ceftas.**
- Cefpodoxime: 50 mg, 100 mg, 200 mg tab, 50 mg/5 ml dry syrup: **Cefoprox, Cepodem.**
- Cefdinir: 300 mg cap, 125 mg/5 ml syrup/dry syrup: **Sefdin, Kefnir.**
- Ceftibuten: 400 mg cap, 100 mg/5 ml dry syrup: **Procadex.**
- Cefditoren: 200 mg tab: **Torocefo, Cefditran, Spectoren.**
- Cefoperazone: 250 mg, 1 gm, 2 gm/vial injection: **Magnamycin,** 1 gm/vial injection: **Megacef.**
- Ceftriaxone: 250 mg, 500 mg, 1 gm/vial injection: **Monocef, Torocef, Ciplacef.**
- Ceftazidime: 500 mg, 1 gm/vial injection: **Fortum, Zidime, Orzid.**
- Ceftizoxime: 250 mg, 500 mg, 1 gm/vial injection: **Cefizox, Eldcef.**
- Cefotaxime : 250 mg, 500 mg, 1 gm/vial injection: **Omnatax, Omnicef, Taxim.**

**Fourth Generation Cephalosporins**

- Cefepime: 500 mg, 1 gm/vial injection: **Ceficad, Cepime, Kefage.**
- Cefpirome : 250 mg, 500 mg 1 gm/vial injection: **Refzil, Bacirom, Forgen.**

## 2.4.3 Chloramphenicol

Chloramphenicol (Chloromycetin) is a broad spectrum antibiotic derived from *Streptomyces venezuelae*. Chemically, it is unique in having a nitro group and a nitrobenzene moiety.

**Mechanism of Action and Resistance:**

It inhibits bacterial protein synthesis by binding to the 50S ribosomal sub-unit. It is bacteriostatic in most pathogens but bactericidal to *H influenzae*. Chloramphenicol-induced inhibition of mitochondrial protein synthesis, by inhibiting eukaryotic mitochondrial 70S ribosomes, probably is responsible for associated host toxicity.

Resistance to Chloramphenicol develops due to following reasons:

- Ribosomal protection which results in decreased affinity for the drug to the ribosomal binding site.
- Decreased permeability to the drug, and
- Production of plasmid as well as chromosomal- mediated Chloramphenicol acetyl transferase which metabolises Chloramphenicol to an inactive form.

**Antimicrobial Spectrum and Clinical Use:**

It is active against a wide range of Gram-negative organisms like *S typhi, H influenza and N meningitides*. It is also active against Gram-positive organisms like *S pneumonia and* most anaerobic bacteria including penicillin-resistant *B fragilis*. It is also active against spirochaetes, rickettsiae, *Mycoplasma and Chlamydia*.

Because of bone marrow depression and aplasia, Chloramphenicol is not justified for minor infections. It is useful for following infections:

- It is preferred for meningitis caused by *H influenza, N meningitides and S pneumonia,* particularly if the patient is hypersensitive to β-lactams. However, third generation Cephalosporins are preferred in this condition.
- Earlier, it was a drug of choice for typhoid fever. Its use has declined due to resistant strains. Being bacteriostatic, it does not cure carrier state and there is relapse in 10% of cases. Other antibiotics used for treating typhoid are Ciprofloxacin, Ceftrixone, Cefoperazone and Cefotaxime.
- It is used for serious anaerobic infections (pelvic and brain abscess) caused by penicillin resistant *B fragilis*. However, Clindamycin and Metronidazole are preferred.
- It is topically used for treating conjunctivitis and external ear infections. When given systemically, it attains high concentration in ocular fluid and hence preferred to treat endothalimitis caused by sensitive strain.

**Pharmacokinetics:**

It is rapidly and completely absorbed after oral administration. Its palmitate salt is used for oral suspension. The salt is degraded into Chloramphenicol by pancreatic lipase in duodenum. It can be administered either orally or by intravenous route. It is widely distributed in different body compartments including CSF. It is metabolised in liver by glucuronyl conjugation and is excreted through urine. Its plasma half-life is 3-5 hours.

**Adverse Effects:**

Following are adverse effects on haematopoietic system:

- Dose-related bone marrow depression.
- Non-dose related idiosyncratic aplastic anaemia.
- Gray baby syndrome (abdominal distension, progressive cyanosis, called gray body, hypothermia, vomiting, loss of hunger and cardiovascular collapse).
- Super-infection.

**Drug Interactions:**

- Paracetamol increases bioavailability of Chloramphenicol by 28%.
- Chloramphenicol is a potent enzyme inhibitor and inhibits metabolism of morphine (causing severe respiratory depression), of Chlorpropamide (causing hypoglycaemia) and of Warfarin (causing bleeding).

**Preparations:**

- Chloramphenicol: 250 mg, 500 mg cap, 125 mg/5ml suspension, 1 gm/vial injection: **Chloromycetin, Paraxin;** 0.4% eye drops, 1% eye ointment: **Paraxin;** (Chloramphenicol 0.5% + Dexamethasone 0.1%) eye drops: **Chlorment-DM, Dexoren-S.**

## 2.4.4 Macrolides

The term Macrolides means a multi-membered lactone ring structure to which one or more deoxy- sugar molecules are attached. The prototype molecule is Erythromycin which has a 14 membered lactone ring attached with two deoxysugar moieties. It is obtained from *Streptomyces erythreus*. The other derivatives are Roxithromycin, Clarithromycin and Azithromycin. All of them are semisynthetic derivatives of Erythromycin. Another derivative Spiramycin is obtained from *Streptomyces ambafaciens*.

**Mechanism of Action:**

Macrolides inhibit protein synthesis by binding reversibly to the "P" (promoter) site of the 50S ribosomal unit of the bacteria. They inhibit the translocation step wherein t-RNA with its growing peptide chain is translocated /shifted from the "A" (acceptor) site to the "P" (promoter) site. See figure 2.2. As a result, the ribosome cannot move on one codon further towards right, relative to m-RNA. Thus, the "A" (acceptor) site, due to inhibition of translocation, does not become free to accept the next incoming t-RNA charged with desired amino acid. The protein synthesis stops as a result of this. They do not inhibit the 60S or 40S ribosomal units of mammaliam cells. They do not permeate through mitochondrial membrane of the host cells. Thus they are selectively toxic only to invading microorganism and not to the host cell.

Antimicrobial activity of these drugs is enhanced by alkaline pH, because these are weakly basic drugs and increased pH results in more unionised form of the drug which facilitates penetration into bacterial cells.

**Resistance:**

Resistance to Macrolides results from modification of the receptor sites on the 50S ribosomes, through a methylation reaction (ribosomal protection) which results in a decreased binding of the drug. Efflux systems represent another mechanism for resistance. Another mechanism of resistance is failure of these drugs to permeate through bacterial cell membrane. Some resistant enteriobacteriacae produce esterases enzymes which hydrolyse Macrolides. Active efflux mechanism and methylase production account for the vast majority of resistant strains in Gram-positive organisms.

**Antibacterial Spectrum:**

Antimicrobacterial spectrum of Macrolides overlaps much with that of Ampicillin. Thus, Erythromycin can be used in patients who are allergic to Penicillins. Macrolides are effective against various organisms as cited below:

- **Gram-positive cocci:** *Streptococcus pneumonia, S pyogenes and Staphylococci.*
- **Gram-negative cocci:** *Neisseria gonorrhoae and Moraxella catarrhalis.*
- **Gram-positive bacilli:** *Corynebacterium diptheriae, Bacillus anthracis, Listeria monocytogenes and Clostridium tetani.*
- **Gram-negative bacilli:** *Legionella pneumophila, Bordetella pertusis, Bartonella henselae, Haemophilus influenza, H ducreyi, Campylobacter jeguni and Helicobacter pylori.*

- **Acid fast bacilli:** *Mycobacterium kansasii, M avium intracellulare, M avium complex, M leprae.*
- **Spirochaetes:** *Treponema pallidum.*
- **Miscellaneous organisms:** *Mycoplasma pneumonia, Ureaplasma urealyticum, Chlamydia trachomatis, Chlamydia pneumonia and Chlamydia psittaci.*

There are some comments about individual Macrolides as cited below:

- The microorganisms cited above are highly sensitive to Erythromycin.
- Strains resistant to Macrolides include *Peptostreptococcus, Actinobacillus, Pasteurella, Fusobacterium, B fragilis, Mycobacterium tuberculosis, H influenza,* MRSA, Enterobacteriacae (including *Salmonella*).
- Roxithromycin has the same spectrum like Erythromycin but it is more potent against *Moraxella catarrhalis* and *Legionella;* and less potent against *Bordetella pertusis.*
- Clarithromycin has increased activity against *Moraxella catarrhalis, Legionella pneumophila, H influenzae and Chlamydia trachomatis* as compared to Erythromycin. In addition, it is highly active against *Mycobacterium avium complex, M leprae, H pylori and Toxoplasma gondii.*
- Azithromycin has higher activity against *H influenzae, Moraxella catarrhalis, Chlamydia trachomatis, Mycoplasma pneumonia, Mycobacterium avium complex, Campylobacter jeguni, H ducreyi and N gonorrhoae* as well as *Toxoplasma gondii* .
- Spiramycin is weaker than Erythromycin. However, it is highly effective against *Toxoplasma gondii and Cryptosporidium.*

**Pharmacokinetics:**

There are special features of different Macrolides as indicated below:

- Erythromycin as a free base is destroyed by gastric acid. Hence it is administered as a enteric coated tablet. Food interferes with its absorption. Ester forms (stearate or ethyl succinate) or ester salts (estolate) are resistant to gastric degradation. Lactobionate is a water soluble salt. It is available for IV/IM injections. IM injections are painful. Empty stomach administration of estolate salt is the best choice.

It is well distributed and produces therapeutic concentrations in tonsilliar tissue, middle ear fluid, lungs and prostatic fluid. It achieves high concentration in alveolar macrophages and neutrophils. CSF levels are 15-20% of plasma levels. It is metabolised by liver and excreted through bile and lost in faeces. Only 5% is excreted in urine, hence does not need dose adjustment in renal failure. Plasma half-life is about 1.5 hours.

- Roxithromycin is a semi-synthetic derivative of Erythromycin. It has a plasma half-life of 12 hours. It is acid stable. Food does not interfere with oral absorption. Due to longer half-life, it is suitable for twice daily dosing.
- Clarithromycin is another derivative of Erythromycin. It is stable towards acid. Food does not interfere with its absorption. Its half-life is 6-7 hours. Daily twice dosing is suitable. It is metabolised in liver to an active metabolite, 14-hydroxyclarithromycin. The drug and its metabolite are excreted through kidney. Dosage adjustments are necessary in patients with renal failure.

- Azithromycin is more acid stable and has wider distribution except for CSF. Therapeutic concentrations are achieved in lung, genital tissue, liver, prostate, phagocytes, macrophages and fibroblasts. Elimination half-life is about 68 hours, which permits once daily dosing and shortening the duration of therapy to 3 days. Food interferes with its absorption. It is administered either one hour before or two hours after meals. It does not inhibit cytochrome P450 enzymes in liver. It is largely excreted unchanged in bile. Renal excretion is only about 5-10%; hence can be given to patients with renal failure. It exhibits significant post-antibiotic effect.
- Spiramycin is incompletely absorbed from GIT. It is given either orally or intravenously. It has high tissue distribution except in CSF. It is metabolised in liver and excreted 90% in the bile and 10% in urine. It is secreted through breast milk. It should be avoided in lactating mother. Its plasma half-life is about 8 hours.

**Therapeutic Uses:**

**Erythromycin:**

It is a first drug of choice for following infections:

- Atypical pneumonia caused by *Mycoplasma pneumonia.*
- Legionnaire's pneumonia.
- Whooping cough due to *B pertussis.*
- Eradication of *Corynebacterium diptheriae* from pharyngeal carriers.

It is second drug of choice for treating following conditions:

- Campylobacter gastro-enteritis (fluoroquinolones are preferred).
- Chancroid due to *H ducreyi.*
- Chlamydial conjunctivitis and urethritis.

Erythromycin is used as prophylaxis against endocarditis during dental procedures in individuals with valvular heart disease; however Clindamycin has replaced it.

It is effectively used to treat acute orofacial infections in dentistry as an alternative to β-lactam antibiotics. The usual dose is 250 mg after every 6 hours.

Erythromycin has anti-inflammatory effects by decreasing pro-inflammatory cytokines released from the phagocytes. It is useful in the management of rheumatoid arthritis, cystic fibrosis, chronic sinusitis and asthma.

It is a agonist for motilin receptor. Hence it is used to improve gastric emptying in cases of diabetic gastro-paresis. Motilin stimulates contraction of stomach leading to enhanced gastric emptying.

**Roxithromycin:**

It is similar to Erythromycin but is preferred for treating otitis media, sinusitis and pneumonia caused by *Moraxella catarrhalis* and pneumonia caused by *Legionella.* It is less potent against *B pertusis (*whooping cough*).* Usual oral dose is 150 mg at the interval of 12 hours.

**Clarithromycin:**

It is similar to Erythromycin but is more effective against *Mycobacterium avium complex* (MAC), *H influenzae, Toxoplasma gondii, M leprae and H pylori.* MAC is a common cause in later stages of AIDS and is difficult to treat. The recommended dose is 200-500 mg BD. It may be combined with Ethambutol (MAC), Minocyclin (leprosy) and Omeprazole (peptic ulcer).

**Azithromycin:**

It is almost similar to Clarithromycin except that it is more active against *H influenzae, Moraxella catarrhalis and Legionella*. It is highly active against *Chlamydia*. It is also useful against MAC in patients of AIDS. It is useful against community acquired pneumonia. Usual daily dose is 500 mg to be given for 3 days.

**Spiramycin:**

It is similar to Erythromycin but restricted only for *Toxoplasma gondii* to prevent transmission of infection from mother to foetus. Usual adult dose is 6-9 MIU in three divided doses for 5 days. For toxoplasmosis, the dose is 2-3 MIU three times a day for 3 weeks, to be repeated after a gap of 2 weeks till parturition.

**Adverse Effects:**

- Allergic reactions expressed as rash, fever, eosinophilia and skin eruptions.
- Cholestatic hepatitis is common with Erythromycin estolate. It is less with Clarithromycin and rare with Azithromycin.
- Severe epi-gastric pain due to stimulation of motilin receptors.
- Reversible ototoxicity leading to hearing loss; tinnitus.
- IV Erythromycin can cause thrombo-phlebitis, which can be minimised by slow rate of infusion.

**Drug Interactions:**

- Erythromycin and Clarithromycin inhibit CYP3A4 isoenzyme leading to increase in serum levels of Theophylline, Carbamazepine, Statins, Warfarin, Pimozide, Terfenadine and Cisapride leading to respective drug toxicities. Azithromycin does not cause this interaction.
- Macrolides decrease Digoxin metabolism by inhibiting the microbial flora responsible for degrading Digoxin.

**Preparations:**

**Erythromycin:**

- As base; 250 mg tab: **Erysafe.**
- As stearate: 250 gm, 500 mg tab, 100 mg/5 ml suspension, 100 mg/ml drops: **Erythrocin.**
- As estolate: 250 mg, 500 mg tab, 250 mg/5 ml dry syrup, 100 mg/ml drops: **Althrocin;** 100 mg, 250 mg tab, 100 mg/5 ml dry syrup: **E-mycin.**

- As ethyl succinate: 400 mg granules, 125 mg/5 ml dry syrup, 100 mg/ml drops: **Erythrocin.**
- Roxithromycin: 50 mg kid tab, 150 mg tab: **Roxibid, Roximol;** 50 mg kid tab, 150 mg tab, 50 mg/5 ml suspension: **Roxy.**
- Clarithromycin: 250 mg, 500 mg tab, 125 mg/5 ml suspension: **Claribid, Maclar, Crixan.**
- Azithromycin: 250 mg, 500 mg tab, 100 mg/5 ml, 200 mg/5 ml suspension: **Azee, Azithral, Zathrin.**
- Spiramycin: 3MIU tab, 0.375 MIU/5 ml suspension: **Rovamycin.**

## 2.4.5 Quinolones

Nalidixic acid is a simple quinolone derivative. Earlier, it was used commonly to treat infections caused by Gram-negative aerobic microorganisms. 98.5% of Nalidixic acid is protein bound. Hence to achieve adequate serum concentration, high dose needs to be given causing severe toxicity. As a result, it has been replaced now. From 1980s, 6-fluorinated -4 quinolones like Ciprofloxacin and its analogue have replaced Nalidixic acid. They are called as Fluoroquinolones. They have broader antimicrobial activity with fewer side effects and relatively slow rate of microbial resistance. Fluoroquinolins are discussed below.

## 2.4.6 Fluoroquinolones (FQs)

General chemical structure of Fluoroquinolones (FQs) is presented in Fig. 2.12. It has –COOH group at position 3, -CO group at position 4 and fluorine at position 6. The –COOH and –CO group offer hydrophobicity and facilitate drug entry into Gram-negative bacteria by passive diffusion while fluorine increases activity against Gram-negative organisms.

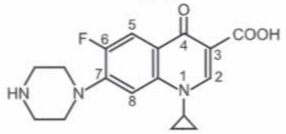



**Fig. 2.12: Structure of Fluoroquinolones**

**Mechanism of Action:**

FQs enter the bacterial cells by passive diffusion through porin channels. Intracellularly, they inhibit the enzyme DNA gyrase (topoisomerase II) and thus prevent replication of bacterial DNA during growth and reproduction. They also inhibit topoisomerase IV, mainly in Gram-positive bacteria. They interfere with the separation of replicated chromosomal DNA into respective daughter cells during cell division.

Inhibition of bacterial DNA gyrase leads to extensive filamentation, vacuole formation and degradation of chromosomal DNA by exonucleases whose production is signalled by damaged DNA. These activities lead to bactericidal action of FQs.

In place of DNA gyrase or topoisomerase IV, the mammalian cells possess topoisomerase II. The mammalian enzyme removes positive supercoiling of eukaryotic DNA to prevent its

tangling during replication. FQs inhibit eukaryotic topoisomerase II only at relatively high concentrations; hence they are selectively toxic to bacteria in therapeutic concentrations.

**Classification:**

Like Cephalosporins, FQs are classified into four generations: first, second, third and fourth generations. They are discussed below.

**Antimicrobial Spectrum:**

**First generation drugs** (eg Ciprofloxacin) demonstrate their activity against following organisms:

- Gram-negative aerobes including enterobacteriaceae (*E coli, Klebsiella, Salmonella, Shigella and Proteus mirabilis*); Gram-negative bacteria like *H influenzae, H ducreyi, Legionella pneumophila, Pseudomonas aeruginosa and Vibrio cholera*.
- Some Gram-negative cocci like *Neisseria gonorrhoeae and N meningitides*.
- They are active against Gram-positive bacilli like *Bacillus anthracis*.
- They have moderate activity against Gram-positive cocci like *Staphylococcus aureus*.
- They are effective against *Mycobacterium tuberculosis, Chlamydia trachomatis and Chlamydia pneumonia.*
- They have no activity against MRSA, *Streptococcus pneumoniae* and anaerobes like *Bacteroides fragilis and Fusobacterium* species. They are not active against *Mycoplasma pneumoniae.*

**Second generation drugs** have similar spectrum to that of first generation drugs with better activity against Gram-positive cocci like *Streptococcus pneumoniae* and other organisms like *Mycoplasma, Legionella and Chlamydia*.

**Third generation drugs** have enhanced activity against Gram-positive cocci like *Streptococcus, Staphylococcus and Enterococcus* as well as for *Mycobacterium tuberculosis, Mycoplasma pneumoniae and M avium complex* in AIDS. They are active against anaerobes also.

**Fourth generation drugs** have enhanced activity against Gram-positive organisms. They have greater activity against anaerobes.

Fluoroquinolones, like Aminoglycosides exhibit concentration-dependent killing and a post antibiotic effect which persists for 3-6 hours. Only fourth generation drugs have dependable activity against anaerobes.

**Resistance:**

Resistance is related to mutations in the DNA gyrase in Gram-negative bacteria and mutations of topoisomerase IV in Gram-negative bacteria.

*Enterococcus, Streptococcus, Pseudomonas aeruginosa, Bacteriodes fragilis* and some *Enterobacteriaceae* display resistance through modification of porin channel and by development of efflux mechanism. All these modes are mediated through chromosomes. There is a possibility of cross-resistance.

**First Generation Fluoroquinolones:**

The examples in this category are: Norfloxacin, Ciprofloxacin, Ofloxacin, Pefloxacin and Lomefloxacin.

**Pharmacokinetics:**

Norfloxacin has poor bioavailability (30-35%). Its plasma levels are not sufficient to treat systemic infections. For other drugs, oral bioavailability ranges from 80-100%. An average protein binding is 20-40%. Tissue penetration is very high. These drugs get concentrated in mucosal tissues of GIT, genitor-urinary and respiratory tract, prostate, lungs, heart and macrophages. They penetrate placental barrier and concentrate in amniotic fluid. They are metabolised in liver and excreted through kidney. Norfloxacin has half-life of 3-5 hours; while Pefolxacin has half-life of 8-10 hours. These drugs are administered twice daily due to their post antibiotic effect.

**Therapeutic Uses:**

Norfloxacin is less potent than Ciprofloxacin and is not used to treat systemic infection due to poor bioavailability. Its use is restricted to urinary, genital and GIT infections only. *Pseudomonas* and Gram-positive cocci are not inhibited by Norfloxacin. Ofloxacin is intermediate between Norfloxacin and Ciprofloxacin in its activity against Gram-negative bacteria. It has slightly better action against Gram-positive organisms and still better action against *Chlamydia and Mycoplasma* as compared to Ciprofloxacin. Pefloxacin penetrates tissues better and accumulates in CSF. It also attains higher plasma concentration due to better bioavailability. Lomefloxacin has a longer plasma half-life and needs single daily dose administration. It is more active against some Gram-negative bacteria and *Chlamydia*.

Various indications and respective dosages are mentioned below:

- Urinary tract infections (UTIs): Norfloxacin, Ofloxacin, Pefloxacin, Lomefloxacin (400 mg BD each), Ciprofloxacin (500 mg BD) orally for 4-6 weeks for lower UTIs.
- Acute bacterial diarrhoea: Norfloxacin (400 mg BD), or Ciprofloxacin (500 mg BD) or Ofloxacin (200 mg BD) orally for 5 days. They are useful in traveller's diarrhoea.
- *Salmonella typhi* infection: Ciprofloxacin (500 mg BD X 10 days), Ofloxacin (400 mg BD X 10 days), Pefloxacin (400 mg BD X 14 days), Norfloxacin (400 mg BD X 14 days).
- Sexually Transmitted Diseases (STDs): Norfloxacin, Pefloxacin (800 mg each), Ofloxacin, Lomefloxacin (400 mg each), and Ciprofloxacin (250-500 mg) all as a single dose for treating *N gonorrhoeae*. For canchroid (caused by *H ducreyi*), Ciprofloxacin (500 mg BD X 3 days) is useful. Ofloxacin (400 mg daily X 7 days) is useful against both *Chlamydia trachomatis and N gonorrhoeae*.
- Soft tissue and wound infections: Ciprofloxacin (500 mg BD X 7 days), Ofloxacin (400 mg BD X 10 days), Pefloxacin (400 mg BD X 7 days) and Lomefloxacin (400 mg OD X 7 days) are used to treat skin and soft tissue infections caused by Gram-negative organisms.

- Respiratory infections: Ciprofloxacin (500 mg BD X 7 days), Ofloxacin (400 mg BD X 10 days), Pefloxacin (400 mg BD X 7 days) and Lomefloxacin (400 mg OD X 10 days) are useful for treating bronchitis and sinusitis caused by Gram-negative pathogens.
- Anthrax: Ciprofloxacin (500 mg BD X 60 days)

**Miscellaneous Uses:**

- Ciprofloxacin and Ofloxacin in combination for *M avium complex* infection in AIDS.
- Pefloxacin is preferred for meningitis due to Gram-negative organisms.
- For chronic bacterial prostatitis: Ciprofloxacin (500 mg BD X 28 days), Ofloxacin (300 mg BD X 42 days) or Pefloxacin (400 mg BD X 28 days).
- Lomefloxacin is preferred for surgical prophylaxis in trans-urethral procedures.
- Ciprofloxacin is used prophylactically in neutropenic patients to minimise Gram-negative bacteraemia.
- Ciprofloxacin is used for cystic fibrosis where *Pseudomonas aeruginosa* is the pathogen.
- All FQs are used as eye drops or ointments for superficial ocular infections.

**Second Generation Fluoroquinolones:**

The examples in this category are Levofloxacin and Prulifloxacin.

- **Pharmacokinetics:** The bioavailability of these drugs is 95-100%. Their protein binding is poor (30-45%) and hence have a wider distribution in body fluids and tissues. Penetration in CSF is relatively poor. Half-life of Levofloxacin is 8 hours while that Prulifloxacin is 10 hours. One single daily dose is adequate. The primary route of elimination is kidney.
- **Therapeutic uses:** Levofloxacin has an extended spectrum of activity against Gram-positive bacteria, especially *Streptomyces pneumoniae,* atypical pathogens like *Chlamydia, Mycoplasma* and also against anaerobes. They are equally effective against Gram-negative organisms like *Pseudomonas, Legionella, Proteus and Moraxella catarrhalis.*

Levofloxacin is mainly used in following conditions:

- Acute bacterial exacerbation of chronic bronchitis.
- Community acquired pneumonia.
- Nosocomial pneumonia.
- Acute sinusitis.
- Uncomplicated skin and soft tissue infections.
- Uncomplicated/complicated UTI.
- Ophthalmic practice as eye drops/ointment for bacterial conjunctivitis and corneal ulcer.

Its usual dose is 500 mg orally, once daily.

Prulifloxacin has an extended spectrum of activity against Gram-negative organisms like *E coli, Pseudomonas, Proteus, Haemophilus, Klebsiella and Moraxella catarrhalis.* It is also active against Gram-positive organisms like *Streptococcus pneumoniae, Enterococcus and Staphylococcus aureus*. It is used for following indications:

- Acute uncomplicated urinary tract infection.
- Complicated lower urinary tract infection, and
- Acute exacerbation of chronic bronchitis.

Its usual oral dose is 600 mg orally, once daily.

**Third Generation Fluoroquinolones:**

The examples in this category are Sparfloxacin, Gatifloxacin and Gemifloxacin.

- **Pharmacokinetics:** All these drugs are readily absorbed from GIT with almost absolute bioavailability. All are widely distributed in body tissues and fluids and are poorly bound to plasma proteins. Gatifloxacin and Gemifloxacin have half-life of 8-10 hours; while Sparfloxacin has a half-life of 18 hours.
- **Therapeutic Uses:** These drugs have enhanced activity against Gram-positive cocci like *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus; Mycobacteria and* anaerobes like *Bacteroids fragilis*. They are primarily used to treat pneumonia, acute sinusitis, exacerbation of chronic bronchitis, UTIs and as an adjuvant drug to treat tuberculosis and also infection of *Mycobacterium avium complex* in patients of AIDS. They are also effective against Chlamydial genital infections like gonococcal urethritis in males.

The usual dose schedule for Sparfloxacin is a loading dose of 400 mg on first day followed by a maintenance dose of 200 mg daily. The dose for Gemifloxacin is 320 mg orally once a day; while that of Gatifloxacin is 400 mg orally, once daily.

**Fourth Generation Fluoroquinolones:**

The examples in this category are Moxifloxacin, Trovafloxacin, Alatrofloxacin and Finafloxacin.

- **Pharmacokinetics:** These drugs are well absorbed orally with a bioavailability of 88-92%. They are primarily metabolised by liver by phase II conjugation. The elimination half-life is longer (10-15 hours) allowing once daily dosing. Trovafloxacin appears in breast milk. Alatrofloxacin is a pro-drug for Trovafloxacin. Alatrofloxacin is usually given intravenously while Trovafloxacin can be given either orally or intravenously.
- **Therapeutic Uses:** Moxifloxacin exhibits enhanced activity against *Streptococcus pneumoniae* and against Penicillin or Erythromycin resistant Gram-positive bacteria and many anaerobes. It retains favourable activity against Gram-negative organisms. It is mainly used for following indications:
  - Community acquired pneumonia.
  - Acute bacterial exacerbations of chronic bronchitis.

- Acute bacterial sinusitis.
- Complicated skin or soft tissue infections.

Its usual dose is 400 mg orally once daily.

Trovafloxacin/Alatrofloxacin is highly active against *Streptococcus pneumoniae,* other Gram-positive bacteria and have an extended spectrum against anaerobes. They have good activity against Penicillin-resistant strains. Due to hepatotoxicity, they are reserved only for life-threatening infections and only for about 15 days. Its use is restricted to treat nosocomial pneumonia, community acquired pneumonia, complicated intra-abdominal infections/gynaecological infections and skin/soft tissue infections including diabetic foot infections. Because of good accumulation in CSF, it is used in cerebral meningitis.

The usual dose is 200 mg IV/orally, once a day.

Finafloxacin is relatively new. It has following characteristics:

- Its anti-bacterial activity increases at acidic pH; thus it becomes more effective in tissues and body compartments, acidified due to infection/inflammation.
- It has no hepato-toxicity, renal toxicity, cardio-toxicity or photo-toxicity.
- It has widest spectrum: Gram-positive, Gram-negative, anaerobic and atypical pathogens.
- It has relatively longer half-life permitting once daily dos

**Adverse Effects to Fluoroquinolones:**

The commonly observed adverse reactions are related to GIT, CNS and cardio-vascular system. The effects are dose dependent. The effects are mild and do not need discontinuation of therapy. Commonest adverse effects are nausea, vomiting, diarrhoea, headache, dizziness and skin rash. Prolonged use can cause tendonitis and tendon rupture.

Other drug specific adverse reactions are as follows:

- Ciprofloxacin; damage to muscle ligaments.
- Lomefloxacin: photo-sensitivity.
- Pefloxacin: photo-sensitivity, hepato-toxicity.
- Sparfloxacin: photo-sensitivity, cardio-toxicity, QTc prolongation.
- Levofloxacin: QTc prolongation.
- Gatifloxacin: QTc prolongation, photo-sensitivity, hyperglycaemia.
- Moxifloxacin: QTc prolongation, photo-toxicity, lowering of seizure threshold.
- Trovafloxacin/Alatrofloxacin : hepato-toxicity.

**Drug Interactions:**

Following drug interactions have been reported:

- Oral absorption of FQs is decreased with $Al^{+++}$, $Mg^{++}$, $Ca^{++}$-containing antacids and also with $Zn^{++}$, $Fe^{++}$ salts as well as Sucralfate. Chelation is the probable cause.
- Plasma concentration of Theophylline is increased by FQs due to inhibition of its metabolism. Levofloxacin and Sparfloxacin has no effect on Theophylline metabolism.

- All FQs interact with Warfarin resulting in its decreased metabolism and enhanced effects. Levofloxacin and Sparfloxacin have no effect on Warfarin metabolism.
- FQs which prolong QTc interval should be used with caution in patient receiving class IA (Quinidine or Procainamide) or class III antiarrhythmics (Amiodarone, Sotalol or Ibutilide) and in patients receiving drugs known to increase QTc interval (Erythromycin, Cisapride, antidepressants, Astemazole and Terfanadine).

Morphine decreases oral absorption of Trovafloxacin.

**Contraindications:**

- Pregnancy and children.
- Drugs which prolong QTc interval are contraindicated in patients with cardiac arrhythmia or those having hypokalaemia.

**Preparations:**

**First Generation FQs:**

- Ciprofloxacin: 250 mg, 500 mg, 750 mg tab: **Cebect, Ciplox, Zoxan, Quintor, Quinobact;** 200 mg/100 ml IV infusion: **Ciplox, Ciprobid, Quintor;** 0.3% eyeointment/drops: **Zoxan, Ciplox.**
- Lomefloxacin: 400 mg tab: **Lomef-400, Lomitas, Floxaday;** 3 mg/5 ml eye drops: **Lomibact-DPS.**
- Norfloxacin: 200 mg, 400 mg tab: **Norflox, Norilet, Uroflox;** 100 mg/5 ml suspension: **Bacigyl;** 0.3% eyedrops: **Norflox-DPS, Norilet-DPS.**
- Ofloxacin: 100 mg, 200 mg, 400 mg tab, 50 mg/5ml suspension, 200 mg/100 ml infusion: **Oflox, Zenflox, Zanocin;** 0.3% eyedrops/ointment: **Oflox, Zenflox-DPS.**
- Pefloxacin : 200mg, 400 mg tab: **Proflox, Pelox;** 0.3% eye drops: **Proflox-DPS.**

**Second Generation FQs:**

- Levofloxacin: 250 mg, 500 mg tab: **Levocide, Levomac, Elvox, Glevo;** 500 mg/100 ml infusion: **Fynal, Glevo, Loxof;** 0.5%, 1.5% eyedrops: **Leeflox-DPS.**
- Prulifloxacin : 600 mg tab: **Alpruli, Puribact, Prulifact.**

**Third Generation FQs:**

- Gatifloxacin: 200 mg, 400 mg tab: **Gabact, Gaity, Gatflox, Gatiquin;** 0.3% eye drops: **Gatilox-DPS, Gatiquin-DPS.**
- Gemifloxacin: 320 mg tab: **Zemi, GQ-320, Gemez.**
- Sparfloxacin : 200 mg tab: **Rexpar, Sparbact, Sparflo, Sparlox;** 0.3% eye drops: **Zospar, Spardrops.**

**Fourth Generation FQs:**

- Moxifloxacin: 400 mg tab, 400 mg/100 ml infusion: **Moxif, Staxom;** 0.5% eye drops: **Mosi-DPS.**

## 2.4.7 Tetracyclines

Tetracyclines, as the name indicates, possess four cyclic anthracycline ring structure. See Fig. 2.13. Different substitutions on these rings alter their pharmacokinetics and also lead to variations in their clinical utility.

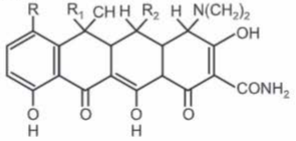



**Fig. 2.13: Structure of tetracycline**

| Type | R | $R_1$ | $R_2$ |
|---|---|---|---|
| Tetracycline | H | $CH_3$ | H |
| Chlortetracycline | Cl | $CH_3$ | H |
| Oxytetracycline | H | $CH_3$ | OH |
| Demethylchlortetracyline | Cl | H | H |

**Mechanism of Action:**

They enter the cytoplasm of Gram-positive bacteria by an energy-dependent active transport system. In Gram-negative bacteria, these drugs pass through the outer membrane by passive diffusion through porin channels. Once inside the bacterial cell, they inhibit the bacterial protein synthesis by binding to their 30S ribosomal sub-unit and block the attachment of aminoacyl t-RNA to the A (acceptor) site of m-RNA ribosome complex. As a result, the peptide chain fails to grow. See figure 2.2. Tetracyclines are bacteriostatic. The carrier involved in active transport of tetracyclines is absent in mammalian cells. These drugs do not bind to mammalian 60S or 40S ribosomal unit. Hence they have selective toxicity only to bacteria.

**Antibacterial Spectrum:**

They are highly active against rickettsia, *Chlamydia psittaci, C trichomatis and C pneumoniae*. They are highly active against spirochaetes like *Borrella burgdorferi and B recurrentis*. Some other atypical pathogens like *Mycoplasma pneumoniae and Ureaplasma urealyticum* are also sensitive to them.

Selective Gram-negative bacteria like *Vibrio cholera, Brucella abortus, Actinomyces israelii, Francisella tularensis, Yersina pestis, Helicobacter pylori and Propionibacterium acnes* are also quite sensitive. Some Gram-positive bacilli like *Bacillus anthracis, Clostridium prefringens and C tetani* are modestly inhibited; however it has no clinical utility.

All Gram-positive and Gram-negative cocci and Gram-negative bacilli like *E coli, Enterobacter, Proteus, Pseudomonas aeruginosa, Klebsiella, Salmonella, Shigella* and *B fragilis* have now become resistant to tetracyclines. *Entamoeba and Plasmodia* are inhibited at higher concentrations.

**Resistance:**

Following four mechanisms contribute to development of resistance for tetracyclines:

- Decreased cell permeability of the drug.
- Increased drug efflux from bacterial cell by an energy-dependent process.
- Ribosomal protection and
- Enzymetic inactivation of the drug.

Amongst these mechanisms, drug efflux is the most common mechanism and there are atleast 300 different efflux proteins which extrude tetracyclines from the bacterial cell.

**Classification:**

Tetracyclines are classified into three groups. They are as follows:

- **Group I:** Shorter acting with half-life of 6-10 hours. Eg: Tetracycline, Chlortetracycline and Oxytetracycline.
- **Group II:** Intermediate acting with half-life of 12-13 hours. Eg: Demeclocycline and Methacycline.
- **Group III:** Long-acting with half-life of 18-20 hours. Eg: Doxycycline and Minocycline.

**Pharmacokinetics:**

They are variably absorbed from GIT with significant differences in bioavailability: Chlortetracycline: (30%); Demeclocycline, Oxytetracycline and Tetracycline (60-80%); Minocycline and Doxycycline (95-100%). Food retards absorbtion of tetracyclines except for Doxycycline and Minocycline.

Tetracyclines are widely distributed throughout the body tissues and fluids except CSF. They get deposited in teeth, bones and in tumours like gastric carcinoma where there is high calcium content. The serum protein binding for tetracyclines is: Tetracycline, Chlortetracycline and Oxytetracycline (20-60%); Demeclocycline and Methacycline (40-80%) and for Doxycycline and Minocycline (80-95%). All of them cross placental barrier.

They are metabolised in the liver and are concentrated in the bile or excreted in urine. Urinary excretion ranges from 70-75% for Tetracycline, Chlortetracycline and Oxytetracycline. Doxycycline and Minocycline are primarily excreted through bile; hence they can be safely administered in patients with renal impairment. Other tetracyclines may accumulate in case of renal failure; if doses are not adjusted, they may cause hepatotoxicity. Minocycline is excreted through saliva and tears. All tetracyclines are secreted through breast milk and should be avoided by lactating mothers.

**Clinical Uses:**

Tetracyclines are the drug of choice for the treatment of Rocky Mountain spotted fever, typhoid fever (*Rickettsia*); psittacosis, granuloma inguinale, pneumonia (*Chlamydia*); non-specific urethritis (*Ureaplasma urealyticum*); atypical pneumonia (*Mycoplasma pneumoniae*); Lyme disease (*Borrelia burgdorferi*) and relapsing fever (*B recurrentis*).

They are also effective in the treatment of brucellosis (*Brucella abortus*), tularaemia (*F tularensis*) and plague (*Y pestis*). In these conditions, tetracyclines are used with Gentamycin. They are also used singularly for bacteraemia and abscesses (*Pasteurella*); trachoma, inclusion conjunctivitis, non-specific urethritis/cervicitis (*C trachomatis*) and for abdominal/thoracic lesions (*Actinomyces israelii*).

In addition, they are also used for amoebiasis (along with Metronidazole), malaria (along with Quinine or Sulphadoxin + Pyrimethamine), acne and peptic ulcer due to *H pylori*.

The recommended daily doses are as follows:

- Oxytetracycline 250 mg 6 hourly.
- Demeclocycline 300 mg 12 hourly.
- Doxycycline 100 mg 12 hourly on first day followed by 100 mg daily.
- Minocycline 100 mg 12 hourly.

Except for Demclocycline and Methacycline, which are given only orally, others can be administered either orally or intravenously.

Doxycycline is preferred for patients with renal disease. Demeclocycline inhibits the actions of ADH in renal tubules and is used in the treatment of excess treatment of ADH. Minocycline 100 mg orally, BD for 5 days is used to eradicate meningococcal carrier state from the nasopharynx. It is also used for swimming pool granuloma (*Mycobacterium marinum*) and for chronic facial dermatosis.

**Adverse Effects:**

- Oral administration can cause nausea, vomiting, epi-gastric burning and somatitis. Chronic use can cause fungal oesophagitis. Superinfection may result in intestinal infection of *Candida albicans*. Over-growth of *Staph aureus and Clostridium difficile* can cause enterocolitis.
- Staining of deciduous and permanant teeth as well as retardation of bone growth occur if tetracyclines are administered during pregnancy or given to children below 10 years.
- Hepatotoxicity may occur in pregnancy. On prolonged use, they may cause elevated blood urea.
- Except Doxycycline and Minocycline, other tetracyclines can be nephrotoxic on prolonged use, and may accumulate in patients with renal dysfunction.
- A special renal toxicity termed Fanconi's syndrome is observed if tetracyclines are used after expiry date. It leads to kidney damage.
- Intravenous injection can cause phlebitis. Intramuscular injection is painful, cause irritation and should be avoided.
- Pulmonary eosinophilic syndrome can occur even with 10 day therapy. The effect is reversible.

- Minocycline causes vestibular toxicity leadigng to vertigo, ataxia. It may induce skin pigmentation. Symptoms resolve after discontinuation.
- Demeclocycline and Doxycycline can induce photo-sensitivity to Sunlight and UV light.
- Demeclocycline antagonises renal actions of ADH and can induce nephrogenic diabetes insipidus.

**Drug interactions:**

- Aluminium, calcium, zinc, magnesium and iron preparations decrease absorption of tetracyclines due to chelation.
- Administration of sodium bicarbonate alters gastric pH and reduces absorption of tetracyclines.
- Enzyme inducers like barbiturates, phenytoin and carbamazepine reduce serum levels of tetracyclines.
- They inhibit intestinal flora which produce vitamin K; therefore they may potentiate anticoagulant effects of Warfarin.

**Contraindications:**

They are contraindicated in renal impairment, hepatic insufficiency, pregnancy, lactation and in children below 10 years of age. Tetracyclines should never be used after expiry date. Intrathecal injections should be avoided.

**Preparations:**

- Demeclocycline: 150 mg, 300 mg tab: **Ledermycin.**
- Doxycycline: 50 mg, 100 mg, 200 mg cap: **Doxy-1;** 100 mg cap: **Lupidox;** 100 mg cap/tab: **Tetradox.**
- Minocycline: 50 mg, 100 mg cap: **Cynomycin.**
- Oxytetracycline: 250 mg, 500 mg cap, 50 mg/ml injection, 3% skin ointment, 1% eye ointment: **Teramycin.**
- Tetracycline : 250 mg, 500 mg tab: **Hostacycline, Resteclin, Subamycin.**

## 2.4.8 Aminoglycosides

The term aminoglycosides indicates presence of aminocyclitol (a non-sugar) linked by a glycoside bond to sugars. In many Aminoglycosides, the aminocyclitol moiety is 2-deoxystreptamine which is placed centrally between two amino sugars as indicated in Fig. 2.14. However in Streptomycin, the aminocyclitol is streptidine which is not placed centrally. It is placed laterally to the aminosugar, ie, streptose, which in turn is joined to another amino sugar ie, N-methyl-L-glucosamine. The structural features of Streptomycin are shown in Fig. 2.15.


**Fig. 2.14: Structure of aminoglycosides**

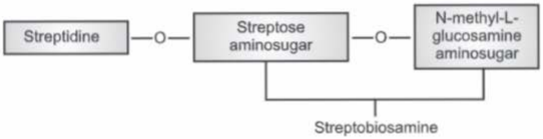



**Fig. 2.15: Structure of streptomycin**

**Mechanism of Action:**

Initially, the Aminoglycosides penetrate through the bacterial cell wall, to preplasmic space, through porin channels by passive diffusion. Subsequently, further transfer of Aminoglycosides across the cytoplasmic membrane takes place by energy and oxygen dependent active transport. Aminoglycosides are inactive against anaerobic bacteria.

These drugs bind to 30S ribosomal unit of the bactetia and prevent formation of "initiation complex" which is prerequisite for peptide synthesis. See figure 2.2. Lack of formation of initiation complex causes the 30S sub-unit to mis-read the genetic code on m-RNA. Incorrect amino acids are thus incorporated into the growing peptide chain, which is of no use for bacterial growth.

Formation of improper initiation complex also blocks the movement of ribosomes, resulting in a m-RNA chain attached with single ribosomes, called as monosomes. Thus Aminoglycosides interfere in the assembly of polysomes, which results in the accumulation of non-functional ribosomes.

**Post-antibiotic Effect:**

Aminoglycosides exhibit concentration-dependent killing. In other words, their increased concentrations kills an increasing proportion of bacteria at a rapid rate. They possess significant post-antibiotic effect that means they continue to suppress bacterial growth for several hours even when their serum concentration falls below MIC. This post-antibiotic effect explains why these drugs can be given in a single daily dose despite their short half-life of 1-3 hours.

Single daily dosing for 4-5 days is justified in most patients having serious infections. However, it is not suitable in following situations:

- In cases of renal insufficiency, where selection of appropriate dose is critical and repeating the dose can be disastrous.
- When Aminoglycosides are given along with β-lactam antibiotics in enterococcal endocarditis.

**Resistance:**

Following three mechanisms are responsible for antibacterial resistance:

- Synthesis of plasmid-mediated bacterial transferase enzymes whcih can inactivate Aminoglycosides. These enzymes are: acetyl transferase, phosphotransferase and adenylyl transferase.

- Decreased transport of Aminoglycosides into bacterial cytoplasm.
- By deletion or alteration of the receptor protein on 30S ribosomal unit because of mutations to prevent attachment of the drug with 30S ribosomal unit.

**Pharmacokinetics:**

They are highly polar, basic drugs which do not permit their membrane permeability. Hence they have poor oral bioavailability. They are given either intravenously/ intramuscularly or as ointments/eyedrops. They are poorly distributed and poorly protein bound. When given parenterally, they fail to reach intraocular fluid or CSF. They do not undergo any significant metabolism. 90-95% of the parenteral dose is cleared by kidney through glomerular filtration. As a result, they have fairly high urinary concentration, which makes them suitable for UTIs. Use of urinary alkaliniser like sodium citrate increases their effectiveness, because they are more active in alkaline pH.

The excretion is directly proportional to creatinine clearance of the patient. In patients with renal insufficiency, the usual half-life of 1.5-3 hours may increase up to 24-48 hours. They are only partially removed by peritoneal or haemodialysis. Dose adjustment is needed in patients with renal insufficiency.

**Antibacterial Spectrum:**

They are primarily directed against Gram-negative aerobic bacilli like *E coli, Klebsiella, Shigella, Proteus* including *Enterobacter and Pseudomonas aeruginosa,* except *Salmonella.* Only a few Gram-positive cocci like *Staphylococcus aureus, Streptococcus viridians and S faecalis* are inhibited. Individual antibiotics differ in their sensitivity towards these organisms. **They are not effective against Gram-positive bacilli, Gram-negative cocci and anaerobes.**

**Individual Drugs and Clinical Uses:**

**Streptomycin:** Ribosomal resistance to Streptomycin develops fast which limits its use.

In plague, tularaemia and brucellosis, it is given in a dose of 1 gm/day intramuscularly in combination with an oral Tetracycline. It is also used with Penicillin for sub-acute bacterial endocarditis (SABE) caused by *Strepto viridans and Strepto faecalis* as well as for bacteraemia. Gentamycin is preferred. Presently, it is kept as a reserve drug among the first line drugs.

**Gentamycin:** It is most commonly used, often in combination with Ampicillin, Benzathene penicillin-G, Ticarcillin, Ceftriaxone and Vancomycin. For septicaemia, sepsis and fever in immunocomprised patients, it is used in combination with penicillins. For pelvic infection, it is combined with metronidazole. For SABE, it is used with Benzarthene penicillin-G. For coliform infection in UTIs, it is combined with Ampicillin or Ceftriaxone. For pseudomonal infection, it is combined with Ticarcillin. It is synergistic with Vancomycin against enterococci. It is useful against enterococcal endocarditis, when patients are allergic to Penicillin.

Its usual dose is 3-5 mg/Kg/day, intramuscularly, in divided doses at 8 hourly intervals for 7-10 days. Single daily dose of 5-7 mg/Kg is equally effective and less toxic. Topically, 0.1-0.3% is used as cream ointment or eyedrops for the treatment of infected burns, wounds and bacterial conjunctivitis. It is inactivated by purulent exudates of wounds. Hence it is not useful in presence of pus.

**Sisomicin:** It is similar to Gentamycin but is more active against *Pseudomonas* and β-haemolytic streptococci. It can be interchanged with Gentamycin. It is resistant to degradation by inactivating enzymes and has no advantage over Gentamycin in terms of toxicity.

**Tobramycin:** It is clinically interchangeable with Gentamycin. It is claimed to be relatively less nephrotoxic. It is useful against infections due to *Pseudomonas, Proteus and Acinetobacter* which are resistant to Gentamycin.

**Netilmicin:** It is semi-synthetic derivative of Sisomicin. It is relatively resistant to inactivating enzymes and is a better alternative to Gentamycin or Tobramycin resistant infections caused by indole-positive *Proteus, Pseudomonas, Klebsiella, E coli and Staph aureus*. The doses and routes of administration are similar to Gentamycin. It is interchangeable with Gentamycin or Tobramycin with similar toxicity.

**Kanamycin:** It is oto-toxic and nephro-toxic. It is no longer used.

**Amikacin:** It is a less toxic, semi-synthetic derivative of Kanamycin. It is resistant to enzymes and hence used against Gentamycin/Tobramycin-resistant Gram-negative bacilli like *Pseudomonas, Proteus and Serratia*. It is also effective in multi-drug resistant *Mycobacterium tuberculosis*, but is used in combination with other anti-tubercular drugs as a second line of therapy. Usual dose is 7.5-15 mg/Kg/day intramuscularly or intravenously in two equally divided doses at 12 hourly interval.

**Neomycin:** It is used either locally. It has a restricted oral use. Leaving aside *Pseudomonas and Stereptococci*, which are resistant, it is active against some Gram-positive and some Gram-negative bacteria. It has following notable features:

- Neomycin with Polymyxin-B solution is used as an irrigant in the urinary bladder to prevent bacteriuria associated with use of indwelling catheter.
- It is combined with Bacitracin and Polymyxin-B to prevent infection in minor cuts, wounds and burns as well as to treat superficial external ear and eye infections. Such combinations are available as ointment or eye/ear drops.
- It is used orally as pre-operative intestinal antiseptic (1 gm TDS or QID) a day before surgery along with Erythromycin (250 mg QID) to reduce aerobic bowel flora.
- It is used in the dose of 1 gm TDS or QID, along with reduced protein intake during hepatic coma. It suppresses ammonia-producing coliform bacterial flora; which prevents brain encephalopathy.

**Framycetin:** It is used as an ointment for skin infections, otitis externa, furunculosis, burns and scalds. Eye drops are used for ophthalmic infections.

**Paromomycin:** In a dose of 1 gm QID orally for two weeks, it can be used to treat intestinal amoebiasis. It is also used orally to treat cryptosporidiosis in immunocompromised patients. It causes watery diarrhoea and abdominal cramps which become severe in AIDS patients.

**Spectinomycin:** It is not a true aminoglycoside chemically. A single dose of 40 mg/Kg intramuscularly can be used as an alternative treatment for gonorrhoea in patients who are allergic to penicillin.

**Adverse Effects:**

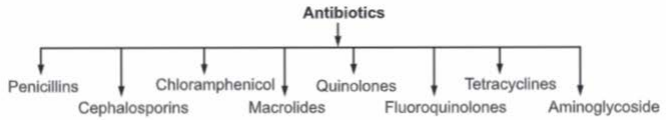
- **Nephrotoxicity:** Neomycin, Gentamycin, Amikacin and Tobramycin are more nephrotoxic than Streptomycin. This toxicity is observed in patients of renal insufficiency, biliary obstruction/hepatitis or when therapy is continued for several days. The toxicity results in increase in creatinine levels above 1.5 mg/dL. Concurrent use of loop- diuretics like Furosemide/ Ethacrynic acid or other nephrotoxic drugs like Vancomycin, Amphotericin-B, Polymyxin-B, Cisplatin and Cyclosporin potentiate the nephrotoxicity. Aminoglycoside induced- nephrotoxicity is nearly reversible.
- **Ototoxicity:** Aminoglycosides cause impairment of $8^{th}$ cranial nerve function. They accumulate in endolymph and perilymph of the inner ear leading to irreversible vestibular and cochlear damage. Vestibular damage leads to vertigo, ataxia and loss of balance; while cochlear damage leads to hearing loss and tinnitus. Vestibular toxicity is more with Streptomycin and Gentamycin while cochlear toxicity is more with Neomycin and Amikacin. Tobramycin has both types of toxicities. Netlimicin has lower toxicity. The ototoxicity is worsened by co-administration of Vancomycin, Furosemide, Ethacrynic acid and reduced by calcium ions.
- **Neuromuscular blockade:** Aminoglycosides cause neuromuscular junction blockade by displacing $Ca^{++}$ from neuromuscular junction and by several other mechanisms like inhibiting acetyl choline release from cholinergic neurons. This block is severe if another skeletal muscle relaxant is co-administered. The blockade can be reversed by intravenous administration of calcium gluconate or intramuscular administration of neostigmine. The neuromuscular blockade is more with Neomycin and Streptomycin as compared to Amikacin, Gentamycin, Tobramycin and Netilmicin.

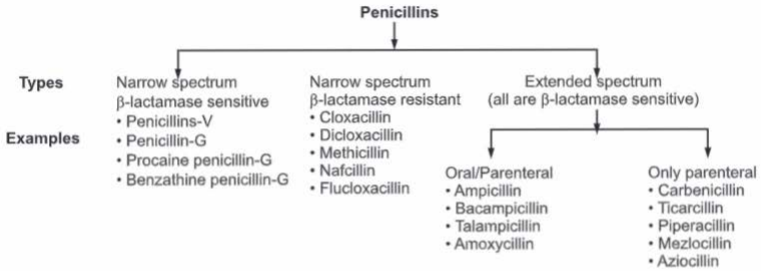
**Preparations**

- Gentamycin: 20 mg, 60 mg, 80 mg/vial injection: **Garamycin, Genticyn;** 0.3% eye/ear drops: **Bactigen, Garamycin, Genticyn.**
- Sisomicin: 10 mg, 50 mg/ml injection: **Sisoptin, Ensamycin;** 0.1% cream: **Ensamycin.**

- Tobramycin: 20 mg, 60 mg, 80 mg/vial injection: **Tobacin, Tobraneg;** 0.3% eye drops: **Toba, Tobacin, Tobrabact;** (Tobramycin 0.3% + Dexamethasone 0.1%) eye drops: **Toba-DM, Tobacin-D, Tomadex.**
- Netilmicin: 10 mg, 25 mg, 50 mg, 100 mg/ml injection: **Netromycin, Netromax.**
- Amikacin: 50 mg, 125 mg, 250 mg/ml injection: **Amister, Nimicin, Ivimicin, Mikacin.**
- Neomycin: 350 mg cap: **Neomycin sulphate;** (Neomycin sulphate 3400 IU + Polymyxin-B 10.000 IU + Hydrocortisone 10 mg)/ml ear drops: **Neosporin-H;** (Neomycin 3,400 IU + Polymyxin-B 5,000 IU + Gramicidin 0.025 mg)/ml eye drops: **Neosporin;** (Neomycin 0.5% + Clobetesol acetate 0.5%) cream: **Clostagen;** (Neomycin 3,400 IU + Polymyxin-B 5,000 IU + Bacitracin 400 IU)/gm ointment: **Neosporin;** (Neosporin 5 mg + Bacitracin 250 IU + Sulphacetamide 60 mg)/gm dusting powder: **Nebasulf.**
- Framycetin : 0.1% eye drops: **Soframycin;** (Framycetin 5 mg + Gramicidin 0.05 mg + Dexamethasone 0.5 mg)/ 5 ml eye/ear drops) **Sofracort;** (Framycetin 1% + Dexamethasone 0.1%) cream: **Sofradex.**

## SUMMARY



## Cephalosporins

| | First generation | Second generation | Third generation | Fourth generation | Fifth generation |
|---|---|---|---|---|---|
| **Types** | | | | | |
| **Examples** | • Cephalexin*<br>• Cefadroxil*<br>• Cephradil**<br>• Cefazolin | • Cefaclor*<br>• Cefuroxime**<br>• Cefprozil*<br>• Cefotetan<br>• Cefamandole<br>• Cefoxitin | • Cefixime*<br>• Cefpodoxime*<br>• Ceftibuten*<br>• Cefdinir*<br>• Cefditoren*<br>• Cefoperazone<br>• Ceftriaxone<br>• Cefotaxime<br>• Ceftazidime<br>• Ceftrizoxime | • Cefpixrome<br>• Cefepime<br>• Cefozopran | • Ceftobiprole<br>• Ceftaroline |

* Oral
** Oral and parenteral
All others are parenteral

## Macrolides

- Erythromycin
- Roxithromycin
- Clarithromycin
- Azithromycin
- Spiramycin

(Salts) → Stearate / Estolate / Ethyl succinate

## Fluoroquinolones

| First generation | Second generation | Third generation | Fourth generation |
|---|---|---|---|
| •Norfloxacin<br>• Ciprofloxacin<br>• Ofloxacin<br>• Pefloxacin<br>• Lomefloxacin | • Levofloxacin<br>• Prulifloxacin<br>• Prulifloxacin | • Sparfloxacin<br>• Gatifloxacin<br>• Gemifloxacin | • Moxifloxacin<br>• Trovafloxacin<br>• Alatrofloxacin<br>• Finafloxacin |

## Tetracyclines

| Short-acting | Intermediate acting | Long-acting |
|---|---|---|
| • Tetracycline<br>• Chlortetracycline<br>• Oxytetracycline | • Demeclocycline<br>• Methacycline | • Doxycycline<br>• Minocycline |

**Aminoglycosides**

- Streptomycin
- Gentamycin
- Sisomicin
- Tobramycin
- Netilmicin
- Kanamycin
- Amikacin
- Neomycin
- Framycetin
- Paromomycin
- Spectinomycin

## REVIEW QUESTIONS

**Long Answer Questions:**

1. Elaborate on sites and mechanism of action of antibiotics.
2. Describe different steps of protein synthesis.
3. What are different mechanisms for bacterial resistance to antibiotics?
4. Describe principles of antibiotic dosing.
5. Describe pharmacology of Sulphonamides.
6. Describe clinical uses of cotrimoxazole.
7. Describe pharmacological actions of penicillins.
8. Describe details of mechanism of action of penicillins.
9. With suitable examples, classify Cephalosporins.
10. What are adverse effects and drug interactions of Cephalosporins?
11. Describe pharmacology of Chloramphenicol.
12. Describe pharmacology of Macrolide antibiotics.
13. Describe various generations of Fluoroquinolines with suitable examples.
14. Describe therapeutic uses of Norfloxacin.
15. Comment on adverse effects of Fluoroquinolines with special reference to individual drugs.
16. Describe pharmacology of tetracyclines.
17. Describe pharmacological actions of aminoglycoside antibiotics.

**Short Answer Questions:**

1. What are dangers of antibiotic therapy?
2. What is post-antibiotic effect (PAE)?
3. Name groups of antibiotics based on CDKE, TDKE and PAE.
4. What is super-infection?
5. What is mechanism of action of Sulphonamides?
6. Classify Sulphonamides based on duration of action.
7. What is antimicrobial spectrum of Sulphonamides?
8. Comment on pharmacokinetics of Sulphonamides.
9. What are adverse effects of Sulphonamides?

10. What are drug interactions related to Sulphonamides?
11. Justify combination of drugs in Cotrimoxazole.
12. Classify penicillins.
13. Comment on pharmacokinetics of penicillins.
14. What are β-lactamase inhibitors?
15. Enlist adverse effects to penicillins.
16. Comment on antagonistic drug interactions related to penicillin.
17. Comment on synergistic combinations related to penicillins.
18. Comment on first generation Cephalosporins.
19. What are special features of third generation Cephalosporins?
20. What is mechanism of action of Chloramphenicol?
21. What is antimicrobial spectrum of Chloramphenicol?
22. Enlist adverse effects to Chloramphenicol.
23. What are drug interactions related to Chloramphenicol?
24. What is mechanism of action of Macrolides?
25. Describe antimicrobial spectrum of Macrolides.
26. What are adverse effects to Macrolides?
27. What are drug interactions of Macrolides?
28. Comment on therapeutic uses of Erythromycin.
29. What is Nalidixic acid?
30. What is mechanism of action of Fluoroquinolones?
31. What is mechanism of action of tetracyclines?
32. What is antimicrobial spectrum of tetracyclines?
33. What are adverse effects to tetracyclines?
34. What are drug interactions related to tetracyclines?
35. What are contraindications related to use of tetracyclines?
36. How Doxycycline/Minocycline differ from other tetracyclines?

37. What is mechanism of action of Aminoglycosides?
38. What is the basis of post-antibiotic effect caused by Aminoglycosides?
39. Comment on resistance to Aminoglycosides.
40. How Neomycin differs from other Aminoglycosides?
41. Comment on nephrotoxicity caused by Aminoglycosides.
42. Comment on toxicity caused by Aminoglycosides.
43. Comment on neuromuscular blockade caused by Aminoglycosides.

*Unit* ...3

# CHEMOTHERAPY-II

Upon completion of this unit, the student should be able to:

- Understand pharmacological actions of anti-tubercular drugs.
- Understand pharmacological actions of anti-leprotic drugs.
- Understand pharmacological actions of anti-fungal drugs.
- Understand pharmacological actions of anti-viral drugs.
- Understand pharmacological actions of anti-helmintic drugs.
- Understand pharmacological actions of anti-malarial drugs.
- Understand pharmacological actions of anti-amoebic drugs.

## 3.1 ANTI-TUBULAR AGENTS

Tuberculosis is caused by *Mycobacterium tuberculosis*. The infection is usually due to inhalation of infected droplet nuclei and lung is the first target organ. Later, the infection disseminates into other organs and the hypersensitivity reaction to microbial proteins may cause extensive tissue damage on any organ. Military tuberculosis is a massive dissemination of *Mycobacterium tuberculosis* throughout the body including liver and spleen which do not have high oxygen tension.

Mycobacteria other than *M tuberculosis* are called as atypical mycobacteria. They are *M kanasii, M marinum, M scrofulaceum and M avium* complex (MAC).

A major portion of tubercle bacilli become intracellular and stay in macrophages. The bacteria are known to develop resistance to any single drug. Hence, combination of drugs is preferred to limit resistance. Response to therapy is slow. Anti-tubercular drugs are divided into two major categories: First line and second line. They are discussed below.

### 3.1.1 First Line Essential Drugs

The therapy normally begins with four first line drugs: Isoniazid + Rifampicin + Pyrazinamide + Ethambutol for two months followed by a course of Isoniazid + Rifampicin for next four months. They can be administered either daily or thrice a week as shown in Table 3.1.

**Table 3.1: Duration and dosage of anti-tubercular drugs.**

| Category and type of patient | Duration of treatment | Drug regimen |
|---|---|---|
| **Category I** | | |
| New (untreated) smear positive pulmonary TB | Intensive phase (2 months) INH + RMP + PZA + ETB followed by: continuation phase (4 months) INH + RMP total 6 months. | |
| New (untreated) smear negative pulmonary TB; seriously ill | | |
| New cases of seriously ill extra-pulmonary TB | | |
| **Category II** | | |
| Smear positive treatment group due to<br>Treatment failure<br>Relapse/default | Intensive phase: (2 + 1 = 3 months) followed by continuation phase (5 months) total 8 months | 2 months: INH + RMP + PZA + ETB + SM; 1 month: INH + RMP + PZA + ETB<br>INH + RMP + ETB |
| **Category III** | | |
| New (untreated) smear negative pulmonary TB; not seriously ill | Intensive phase (2 months) followed by | INH + RMP + PZA |
| | Continuation phase (4 months) total 6 months | INH + RMP |

INH: Isoniazid; RMP: Rifampicin; PZA: Pyrazinamide; ETB: Ethambutol; SM: Streptomycin.

**(1) Isoniazid (INH):** Isoniazid (Isonicotinic acid hydrazide; INH) is a potent synthetic anti-tubercular drug with structural resemblance to pyridoxine.

**Mechanism of Action and Resistance:**

INH inhibits the synthesis of mycolic acids, which are essential components of mycobacterial cell wall along with peptidoglycan. It is pro-drug and the mycobacterial enzyme catalase peroxidise converts it to biologically active form to block the synthesis of mycolic acid. The drug is bactericidal to actively growing tubercle bacilli but not to dormant organisms which are only inhibited. It is primarily an anti-tubercular drug against *M tuberculosis* and *M kanasii*. It acts on both extracellular and intracellular bacilli. It is equally active in acidic and alkaline medium.

The most common mechanism of INH resistance is the mutation in catalase-peroxidase gene responsible for activation of INH. Another mechanism is through mutation in the promoter gene *inh*A involved in biosynthesis of mycolic acid.

**Pharmacokinetics:**

It is well absorbed orally and gets readily distributed in pleural, peritoneal and synovial fluids. CSF concentrations can reach upto 100% if the meninges are inflamed. It is metabolised in liver by the enzyme N-acetyl transferase; the resultant product is acetyl isoniazid. Genetic variants have been observed in its rate of N-acetylation. They are rapid acetylators with plasma half-life of 1 hour and slow acetylators with a plasma half-life of 3 hours. 70% of Indians are slow acetylators. The acetylator status of an individual may influence the nature of INH toxicity but not the anti-tubercular response. It happens because plasma concentration normally remains above MIC.

**Adverse Effects:**

Peripheral neuritis and hepatotoxicity are the two major but, acetylator status-dependent adverse effects. Peripheral neuritis involves paresthesias and numbness. It is more common with slow acetylators. This neurotoxicity can be prevented by prophylactic use of vitamin $B_6$ in a dosage of 10-40 mg/day. Hepatotoxicity is higher above age group of 50-65 years, in persons with liver disease, in alcohol drinkers and in fast acetylators. The metabolites acetyl isoniazid and acetyl hydrazine are more hepatotoxic. The drug should be discontinued at the onset of symptoms like nausea, loss of appetite, abdominal pain and rise in level of amino-transferase enzymes.

Other adverse effects include allergic reactions (fever, rashes), xerostomia, haematological changes and convulsions in seizure-prone patients. Drug-induced systemic lupus erythromatosis has been reported.

**Drug Interactions:**

1. Aluminium hydroxide (from antacids) inhibit absorption of INH.
2. Alcohol increases the risk of hepatitis.
3. INH inhibits the metabolism of Phenytoin and Carbamazepine.

**Dose:**

Typical adult oral dose is 300 mg once daily. If given twice weekly, it should be changed to 600 mg thrice a week. For serious infections or meningitis, 600 mg once daily should be given orally. Duration of treatment is related to the drug-combination.

**(2) Rifampicin (Rifampin; RMP):** It is a semi-synthetic derivative of a macrocyclic antibiotic, Rifamycin.

**Mechanism of Action and Resistance:**

It binds to and inhibits bacterial DNA-dependent RNA polymerase. As a result, new RNA is not synthesised. Mammalian RNA polymerase does not bind to the drug. Hence RNA synthesis of host cells is not affected. The drug is bactericidal for both intracellular and extracellular *M tuberculosis*. In addition, it is also active against *M leprae, Staph aureus, N meningitides, H influenzae, Brucella and Legionella*. It has good sterilising and resistance-preventing action, when used along with other drugs. Rifampicin resistance results from a point mutation in rpoB gene, present on β-sub-unit of RNA polymerase thus preventing binding of the drug to RNA polymerase. Hence, if used alone, resistance develops rapidly.

**Pharmacokinetics:**

It is well absorbed after oral administration. It penetrates in all tissues, tubercular cavities, placenta and is significantly protein bound. Adequate CSF levels are achieved if meninges are inflamed. It is excreted mainly through liver into bile and undergoes enterohepatic circulation. It is a potent enzyme inducer.

**Dose and Clinical Use:**

Its usual anti-tubercular dose is 600 mg single dose before breakfast. When given thrice a week, the same dosage should be maintainted. It is recommended in following indications:

1. Treatment of leprosy along with Dapsone.
2. Prophylaxis of meningococcal (600 mg BD for 2 days) and H influenzae-induced meningitis (600 mg/day for 4 days) and carrier state.
3. For prosthetic valve endocarditis; and
4. For treating brucellosis, along with Doxycycline.

**Adverse Effects:**

Hepatitis is the major adverse effect and the risk is increased when used with INH and in patients with underlying liver disease. Fortunately, it is dose dependent and reversible. Occasional adverse effects include rashes, GI disturbances, dizziness, fatigue and flu-like syndrome characterised by fever, chills, myalgia and thrombocytopenia. It imparts a harmless red orange colour to urine.

**Drug Interactions:**

It induces isoforms of cytochrome P450 enzymes. It accelaerates metabolism of several drugs like oral contraceptives, anti-coagulants and protease inhibitors used in HIV patients, which may result in therapeutic failure.

**(3) Ethambutol (ETB):** It is a synthetic tuberculostatic drug active against *M tuberculosis, M kanasii and M avium-intracellulare.*

**Mechanism of Action:**

It inhibits the enzyme arabinosyl transferase resulting in prevention of polymerisation of arabinoglycans, which are needed for synthesis of mycobacterial cell wall. The drug resistance occurs due to point mutations in the *embB* gene which encodes the arabinosyl transferase enzyme involved in mycobacterial cell wall synthesis. Oral bioavailability is about 80%. It is widely distributed in all body fluids including CSF.

**Doses and Clinical Use:**

It is commonly used along with INH, Rifampicin and Pyrazinamide. If used alone, resistance develops rapidly. Usual daily oral dose is 800-1000 mg. It can be given in a dose of 1600 mg/day thrice a week orally. It is also used in combination with Clarithromycin and Rifabutin in the treatment of *M avium-intracellulare* infection in AIDS patients. Higher doses are needed to treat tuberculous meningitis.

**Adverse Effects:**

If used for more than 9 months, it can cause retrobulbar neuritis impairing visual acuity and red-green colour discrimination. This adverse effect is dose related and reverses slowly after discontinuation of drug. Periodic visual acuity testing is desirable during treatment. It should be avoided in children below 5 years. It decreases renal excretion of urates and may precipitate gouty arthritis. Mild GIT intolerance, rashes, fever and dizziness are also possible.

**(4) Pyrazinamide (PZA):** It is pyrazine derivative of nicotinamide. It is hepatotoxic. In reduced doses, it is an important component of anti-tubercular therapy.

**Mechanism of Action:**

It enters *M tuberculosis* by passive diffusion and is converted to an active metabolite, pyrazinoic acid by bacterial pyrazinamidase enzyme. The active metabolite inhibits mycobacterial fatty acid synthase-I enzyme and disrupts mycolic acid synthesis needed for cell wall. It is bactericidal to *M tuberculosis* and is active at acidic pH. It is highly active on intracellular mycobacteria. A mutation in the gene *pcn*A which encodes pyrazinamidase enzyme is responsible for drug resistance which can be minimised by using drug combination therapy.

**Pharmacokinetics:**

It is well absorbed after oral administration and is widely distributed in all tissues, macrophages, tubercular cavities and in meninges. Its plasma half-life is 9-10 hours.

**Adverse Effects:**

It is hepatotoxic. It may cause hyperuricaemia and precipitate gouty arthritis. Other adverse effects include nausea, vomiting, anorexia, fever and malaise. It should be avoided during pregnancy.

**Dose:**

The dose is 1500 mg orally once a day. It can also be given in two equally divided doses. When given thrice a week, the dose can be increased to 2000 mg/day.

## 3.1.2 First Line Supplemental Drugs

**(1) Streptomycin (SM):** It is bactericidal against *M tuberculosis*. Due to poor penetration, it acts only on extracellular tubercular bacilli. It is also active against *M kanasii* and *M avium intracellulare*. It is less effective than INH and Rifampicin. It has to be given intramuscularly. Resistance develops rapidly if it is used alone. Hence, other first line drugs are given orally and simultaneously in order to prevent emergence of resistance. The resistance is related to a point mutation of genes *rpsl* or *rrs*; which code for ribosomal proteins and ribosomal t-RNA respectively. Mechanism of action and toxicity is given in section 2.1.3.8. as one of the aminoglycoside antibiotic.

Dose per day is 1000 mg intramuscularly which can be reduced to 500-750 mg in elderly and in patients with renal insufficiency. The dosage could be same even if it is used thrice a week. Nephrotoxicity and ototoxicity are the major limitations; hence it is kept in reserve only in life threatening tuberculosis or in situations where any of the first line drug is contraindicated.

**(2) Rifabutin (Mycobutin):** It is a structural analogue of Rifampicin with similar mechanism of action, spectrum of activity and mechanism of resistance. There is a cross-resistance between Rifabutin and Rifampicin.

Rifabutin differs from Rifampicin in following features:

- It is a less potent enzyme inducer of cytochrome P450 enzymes. Hence drug interactions with anti-HIV drugs are minimised.
- It has better activity against *M avium* complex (MAC).
- It is also active against Rifampicin-resistant strains like *M leprae and M fortuitum* and
- It has a longer plasma half-life of 48 hours.

It is used either alone or in combination with Pyrazinamide in the treatment of latent tubercular infection. It can be used in place of Rifampicin, both in the treatment of tuberculosis or HIV-infected patients. The advantage of Rifabutin is in prevention and treatment of disseminated MAC. Recommended dosage is 300 mg/day.

**Adverse effects:** Include skin rash, GI intolerance, neutropenia, hepatitis and red-orange discolouration of urine. It is an enzyme inducer and may decrease plasma concentrations of Theophylline, oral anti-coagulants, protease inhibitors and non-nucleoside reverse transcriptase inhibitors; but the effects are lesser than Rifampicin. Fluoconazole increases Rifabutin plasma concentration resulting in pseudo-jaundice and poly-myalgia syndrome.

**(3) Rifapentine:** It is a structural analogue of Rifampicin with a plasma half-life of 13-15 hours. Its mechanism of action, cross-resistance, enzyme induction, toxic profile and clinical use is similar to that of Rifampicin. It is not used alone but is used in combination with other first line anti-tubercular drugs. Recommended dose is 600 mg orally once or twice weekly. It inhibits CYP3A4 isozyme, but its potential for drug interaction is lower than Rifampicin but higher than Rifabutin.

### 3.1.3 Second Line Drugs

In case, if there is resistance to first line essential/supplementary drugs, then following second line drugs can be added in the treatment of tuberculosis.

**(1) Fluoroqiunolones:** They are important in treatment of *M tuberculosis*, especially in multi-drug-resistant strains. Ciprofloxacin, Ofloxacin, Levofloxacin and Moxifloxacin inhibit 90-95% of the strains of susceptible tubercular bacilli including MAC and *M fortiutum*. Due to better penetration into the cells, they are capable of killing intracellular pathogens. Because of convenient dosage schedule and good tolerance, they are preferred in combination regimens against multi-drug-resistant tuberculosis and MAC infection in patients of AIDS. These can be substituted in combinations if any of the first line drugs are contraindicated.

The recommended doses for Ciprofloxacin are 750 mg BD orally, or 500 mg TDS; for Ofloxacin, the doses are 400 mg BD orally. Levofloxacin is levo-isomer of Ofloxacin and is preferred because of its potency and once daily dosage schedule of 500 mg. Moxifloxacin is given as 400 mg once daily. Moxifloxacin with other drugs reduces the duration of therapy for drug-susceptible tuberculosis.

**(2) Amikacin:** It is an aminoglycoside with significant ototoxicity and nephrotoxicity. Hence it is considered as a second choice after Streptomycin and Capreomycin. It is useful in treatment of MAC in patients of AIDS. Strains of *M tuberculosis* which are resistant to Streptomycin, are sensitive to Amikacin. The recommended dose is 15 mg /Kg/day IM or IV for 5 days a week for 2 months and then 1 gm/day thrice weekly for another 4 months.

**(3) Capreomycin:** It is a tuberculocidal polypeptide antibiotic. It is effective against *M tuberculosis, M kanasii and M avium.* Since it is poorly absorbed from GIT, it has to be given intramuscularly. Adverse effects are similar to those of Aminoglycosides including ototoxicity and nephrotoxicity. The drug is rarely used. It is an important drug for multi-drug resistant tuberculosis.

**(4) Ethionamide:** It is rarely used. The dose is 1 gm/day. It is less tolerated because of intense gastric irritation and neurological toxicity in the form of peripheral neuritis and even optic neuritis. It is also hepatotoxic. The daily dose is 500-750 mg and leads to faster resistance. It blocks the synthesis of mycolic acids and is a tuberculostatic drug.

**(5) Para-Aminosaclicylic Acid (PAS):** It is a structural analogue of PABA. It exhibits bacteriostatic action against *M tuberculosis* by inhibiting folate synthesis of the mycobacterium. Its use has declined due to availability of better and safer alternative. It causes GIT intolerance. Hypersensitivity reactions include skin rashes, lupus-like reactions, drug fever, joint pain and hepatitis. Recommended doses are 8-12 gm/day orally in 2-3 divided doses.

**(6) Cycloserine:** It is broad spectrum antibiotic which acts by inhibiting bacterial cell wall synthesis. It is tuberculostatic to *M tuberculosis* and is also effective against *E coli, Staph aureus, Enterococcus, Nocardia and Chlamydia.* It is readily absorbed after oral administration and is mainly excreted unchanged by the kidney. It is useful against multi-drug-resistant tuberculosis. Usual oral dose is 500 mg BD. Adverse reactions include peripheral neuropathy, dizziness, tremors and psychotic behavioural changes. Neurotoxicity can be reduced by 100 mg/day of vitamin $B_6$ (pyridoxine).

**(7) Thiacetazone:** It is no longer used now because of its ototoxicity and life-threatening hypersensitivity reactions like hepatitis, neutropenia and thrombocytopenia.

**Treatment of Tuberculosis:**

One of the main reasons for therapeutic failure of the treatment of tuberculosis is poor compliance of the patient. To correct this, WHO has recommended Directly Observed Therapy using Short-course (DOTS) where in the anti-tubercular drugs are given under the direct supervision of the medical professional three days a week. India has adopted DOTS therapy and is reflected in Revised National Tuberculosis Control Programme (RNTCP). The schedule of drugs is given in Table 3.1.

As indicated in the Table 3.1, the treatment consists of two phases: intensive phase and continuation phase. Intensive lasts for a period of 2-3 months and is aimed to rapidly kill the bacteria, to minimise the chances for developing resistance to bring about sputum conversion and symptomatic relief. The continuation phase lasts for 4-6 months in which the remaining bacilli are eliminated to minimise the chances of relapse.

In category I patients, use of 3-4 drugs during intensive phase reduces the risk of developing resistance. When most of the bacilli are killed, only two drugs used in continuation phase are enough for the expected effect. In extra-pulmonary tuberculosis and in smear-negative pulmonary tuberculosis patients (category III), there are fewer bacilli in the lesions as compared to seriously ill patients of category I. As a result, the risk of bacterial resistance is low. The use of three drugs in the intensive phase followed by two drugs in the continuation phase can be equally effective. In category II, the relapse/retreatment group requires longer intensive phase with five drugs for two months followed by four drugs for one month. In continuation phase, three drugs are used for five months. Thus, the total duration of therapy is 8 months instead of 6 months.

Multi-drug- resistant category indicates resistance to INH or INH + RMP or more number of drugs. This stage is difficult to cure. Association of other diseases like AIDS/diabetes/silicosis further complicates the problem. If the sensitivity of TB bacilli is known, then the drugs to which bacilli are resistant can be excluded and other first line drugs are prescribed in following schedule:

- For INH resistance: RMP + PZA + ETB for 12 months.
- For RMP resistance: INH + PZA + ETB for 12 months.
- For both INH + RMP resistance: PZA + ETB + SM (or Ethionamide) + Ciprofloxacin/Ofloxacin/Levofloxacin for 12-18 months.

Chemoprophylaxis is indicated to household members and other close contacts of potentially infected patients in the family or to neonates of tubercular mother. In such cases, following regimen is recommended:

- INH 300 mg/day for children, for 6-12 months.
- INH (5 mg/Kg/day) + RMP (10 mg/Kg/day) for 6 months.

In pregnant or breast feeding mothers with tuberculosis, INH, RMP, PZA or even ETB are safe. ETB may be added only during last trimester and not initially. Treatment should not be withheld because of pregnancy. Full course should be given to lactating mother but an infant should receive INH as prophylaxis.

Corticosteroids should not be used in TB patients and should never be given in intestinal tuberculosis due to fear of perforation. They may be used in special circumstances under adequate chemotherapeutic cover as indicated below:

- In patients of AIDS with serious illness.
- In meningeal or renal tuberculosis or pleural effusion, to minimise inflammation and exudation.
- If hypersensitivity reaction occurs during therapy of TB.

Corticosteroids if used, should be gradually withdrawn when the condition of the patient improves.

**Drugs Active against M avium Complex (MAC) in AIDS**

Macrolide antibiotics viz Clarithromycin (500 mg BD orally) and Azithromycin (500 mg OD orally) are very active against *M kanasii, M fortuitum, M marinum and M avium* complex (MAC). They have a limited activity against *M tuberculosis*. They are useful for prevention and treatment of MAC in patients of AIDS.

**Preparations:**

- Isoniazid (INH): 100 mg tab: **Isonex;** 300 mg tab: **Isonex forte;** (INH 300 mg + Pyridoxine 10 mg) tab: **Isokin-300.**
- Rifampicin: 150 mg, 300 mg, 450 mg, 600 mg cap, 100 mg/5 ml suspension: **R-Cin;** 300 mg, 450 mg, 600 mg tab/cap: **Zucox;** 450 mg tab, 150 mg, 300 mg, 450 mg cap, 100 mg/5 ml suspension: **Rimactane.**
- Ethambutol: 200 mg, 400 mg, 600 mg, 800 mg, 1 gm tab: **Combutol;** 400 mg tab, 200 mg, 400 mg, 600 mg, 800 mg, 1 gm cap: **Mycobutol.**
- Pyrazinamide: 500 mg, 750 mg, 1 gm tab: **P-Zide, Pyzina;** 250 mg DT-tab, 500 mg, 750 mg, 1 gm tab, 5% suspension: **PZA-Civa.**
- Combipack: (1 cap Rifampicin 450 mg + 2 tabs Pyrazinamide 750 mg + 1 tab Ethambutol 800 mg + 1 tab Isoniazid 300 mg) kit, 1 day dose: **AKT-4, Mycodox-4, 4-D;** (Rifampicin 600 mg +Isoniazid 300 mg) tab: **R-Cinex;** (Ethambutol 600 mg or 800 mg + Isoniazid 300 mg) tab: **Myconex 600/800.**
- Capreomycin: 500 mg, 750 mg, 1 gm injection: **Kapocin.**
- Ethionamide: 250 mg tab: **Ethide, Mycotuf.**
- Para-amino salicylic acid (PAS): 100 gm granules: **Q-PAS.**
- Thiacetazone : (Thiacetazone 150 mg + Isoniazid 300 mg) tab: **Isokin-T Forte.**

## 3.2 ANTI-LEPROTIC AGENTS

Leprosy is a chronic granulomatous infection caused by an acid-fast bacilli *Mycobacterium leprae*, which is related to tubercle bacilli. *M leprae* cannot be grown on culture media. The organism lies within the macrophages and remains dormant but alive. Hence clinical leprosy is a consequence of deficient cell-mediated immunity in susceptible individuals. Infection is usually transmitted from person to person when bacilli are shed from the nose and skin lesions of the infected patients. The disease affects peripheral nervous system, the skin and various tissues.

Leprosy is classified in two types: Paucibacillary leprosy and multibacillary leprosy.

**Paucibacillary leprosy** is of non-infectious type with few bacilli. It is also called as tuberculoid leprosy.

**Multibacillary leprosy** is an infectious leprosy with numerous bacilli. It is also called as lepromatous leprosy.

**Classification:**

It is divided into four classes as follows (examples are indicated for every class):

- Sulfones: Dapsone.
- Phenazine: Clofazimine.
- Antitubercular drugs: Rifampicin.
- Antibiotics: They are of three types as mentioned below:
  - Fluoroquinolones: Ofloxacin, Sparfloxacin, Pefloxacin.
  - Macrolides: Clarithromycin.
  - Tetracycline: Minocycline.

**Individual Drugs:**

**Dapsone:** It is closely related to sulphonamides and shares a common mechanism of action, i.e., inhibition of bacterial folic acid synthesis. Thus it is leprostatic. It is the most widely used drug for both types of leprosy. If used alone, resistance emerges in some population, especially in case of lepromatous leprosy. Hence it is usually conbined with Rifampicin and/or Clofazimine. The usual adult dose is 100 mg/day orally for 3-5 years. It is also useful in the treatment and prevention of *Pneumocyctitis carinii* pneumonia in patients of AIDS. For prophylaxis, 100 mg/day can be used. For treatment, Dapsone 100 mg/day is combined with Trimethoprim 15-20 mg/Kg/day for 21 days.

It is well absorbed after oral administration and is widely distributed throughout the body fluids and tissues. It tends to remain in skin, muscle, kidney and liver upto 3 weeks after therapy is stopped. Skin heavily infected with *M leprae* may contain 10-15 times higher Dapsone as compared to normal skin. It is acetylated in liver, excreted in bile and undergoes entero-hepatic circulation. About 70% is excreted in urine. Its plasma half-life is 1-2 days.

It may produce non-haemolytic anaemia and methaemoglobinaemia in persons having G6PD deficiency. The drug should be avoided if haemoglobin level is less than 7 gm%. Other adverse effects include nausea, loss of appetite, pruritus, drug fever, reversible neuropathy and hepatotoxicity.

In case of lepromatous leprosy, "lepra reactions" are observed. They are of two types: type 1 lepra reactions and type 2 lepra reactions. Type 1 reactions are delayed hypersensitivity reactions to antigens of *M leprae*. It exhibits as cutaneous ulceration and multiple nerve involvement. It can also be seen in tuberculoid leprosy. Prompt treatment with corticosteroids is advised to prevent nerve damage. Type 2 reactions are also called as erythema nodosum leprosum. It represents a humoral antibody response to dead bacteria. It is of abrupt onset, existing lesions enlarge, become red, inflamed and painful. This reaction can be treated with Clofazimine or corticosteroid or Thalidomide. Clofazimine is slower in comparison to corticosteroids or Thalidomide. It suits for mild type 2 reactions only.

**Clofazimine:** It is a phenazine dye which binds preferentially to mycobacterial DNA to inhibit mycobacterial growth. It is a leprostatic drug with anti-inflammatory property. It is very useful in the treatment of lepra reactions (erythema nodosum leprosum).

It is used for Dapsone-resistant leprosy or in patients who are intolerant to Dapsone. Recommended dose is 50-100 mg/day orally. The antileprotic effect of Clofazimine has a biological lag of 6-7 weeks. Hence it is preferred as a component of multidrug therapy.

Its oral absorption is variable. Major elimination is through faeces. Its plasma half-life is 60-70 hours. It is widely distributed in tissues including phagocytes.

There are two major adverse effects: Red-brown discolouration of skin, especially in people with fair complextion. It causes abdominal pain with loose stools due to deposition of the drug crystals in the intestinal mucosa. It should be avoided in pregnancy. Mild adverse effects include conjunctival pigmentation and phototoxicity.

**Rifampicin:** It is bactericidal to *M leprae*. It rapidly renders leprosy patients non-contagious by killing 99.99% of the organisms within 5-6 days; but resistance develops after prolonged treatment. Hence it is a component of multidrug therapy so that duration can be reduced. Usual daily oral dose in lepromatous leprosy is 600 mg/day; but single 600 mg/month dose is preferred in combination therapy in order to reduce hepatotoxicity and the chance of enzymatic induction.

**Fluoroquinolones:** Ofloxacin in a oral dose of 400 mg/day as a single drug kills 99.9% of *M leprae* within a period of three weeks. However, it is used as an alternative drug for the patients who have Rifampicin intolerance or resistance. Alternatively, Pefloxacin in a oral dose of 400 mg BD or Sparfloxacin in a oral dose of 400 mg on first day, followed by 200 mg/day are highly active.

**Clarithromycin:** It has a weaker activity than Rifampicin against *M leprae*. It is the only Macrolide antibiotic with antileprotic activity. In a oral dose of 500 mg/day, it can kill 99.9% of bacteria in a period of 8 weeks. It is an alternative drug for treating leprosy.

**Minocycline:** It is one of the tetracyclines with activity against *M leprae*. It is less active than Rifampicin but more active than Clarithromycin. If Clofazimine cannot be used because of its adverse effects, then Minocycline in a dose of 100 mg/day can be substituted in standard regimen.

**WHO Regimen**

- **For multibacillary (lepromatous) leprosy:** (Dapsone 100 mg daily + Clofazimine 50 mg daily) for 29 days followed by 300 mg on $30^{th}$ day (29 + 1 days) + Rifampicin 600 mg once a month for 24 months.
- **For paucibacillary (tuberculoid) leprosy:** Dapsone 100 mg daily + Rifampicin 600 mg, once a month is to be given for 6 months. If Dapsone is not tolerated then, Clofazimine 50 mg daily for 29 days should be followed by 300 mg on $30^{th}$ day (29 + 1 days) may be substituted in place of Dapsone.
- **Alternative regimen for multibacillary leprosy:**
  (a) If Rifampicin is not suitable because of resistance or intolerance, then Clofazimine 50 mg daily + Ofloxacin 400 mg daily + Minocycline 100 mg daily should be given for first 6 months; thereafter, Clofazimine 50 mg daily + Ofloxacin 400 mg daily or Minocycline 100 mg daily should be followed for 18 months.

(b) When Clofazimine cannot be given because of skin pigmentation or abdominal pain, then Dapsone 100 mg daily + Ofloxacin 400 mg daily or Minocycline 100 mg daily + Rifampicin 600 mg once a month should be given for 24 months.

**Preparations:**

- Dapsone: 25 mg, 50 mg, 100 mg tab: **Dapsone.**
- Clofazimine: 50 mg, 100 mg cap: **Clofozine, Hansepran.**
- Thalidomide: 50 mg, 100 mg cap: **Thycad, Thaloda.**
- Rifampicin: 150 mg, 300 mg, 450 mg, 600 mg cap, 100 mg/5 ml suspension: **R-Cin;** 300 mg, 450 mg, 600 mg tab/cap: **Zucox;** 450 mg tab, 150 mg, 300 mg 450 mg cap, 100 mg/5 ml suspension: **Rimactane.**
- Ofloxacin: 100 mg, 200 mg, 400 mg tab, 50 mg/5 ml suspension, 200 mg/100 ml infusion: **Oflox, Zenflox, Zanocin.**
- Pefloxacin: 200 mg, 400 mg tab: **Proflox, Pelox.**
- Sparfloxacin: 200 mg tab: **Rexpar, Sparbact, Sparflo, Sparlox.**
- Clarithromycin: 500 mg, 125 mg/5 ml suspension: **Claribid, Maclar, Crixan.**
- Minocycline: 50 mg, 100 mg cap: **Cynomycin.**

## 3.3 ANTI-FUNGAL AGENTS

Fungal infections are called as "mycoses". Fungi have rigid cell wall composed mainly of chitin (instead of peptidoglycan), followed by a cell membrane which consists of ergosterol (unlike cholesterol in mammalian membrane). Fungi are divided into four major classes as follows:

1. **Yeasts:** They reproduce by budding. The only pathogenic yeast is *Cryptococcus neoformans*, which causes meningitis.
2. **Yeast like fungi:** They grow partly like yeast and partly like filaments called hypae. The pathogenic fungus in this group is *Candida albicans* which causes oral/vaginal thrush and systemic candiasis. Another example in this category which causes superficial mycosis is *Pityrosporom orbiculare*, which causes pityriasis vesicolor or tinea vesicolor.
3. **Moulds:** These are filamentous fungi which reproduce by forming spores. Pathogenic moulds are called as dermatophytes. The examples are *Trichophyton, Microsporum and Epidermophyton*, all causing skin or nail infections called tinea or ringworm. This infection is further sub-classified according to body site eg *Tinea barbae* (beard), *T capitis* (scalp), *T corporis* (body), *T cruris* (groin), *T manuum* (hand), *T pedis* (athlete foot) and *T unguium* (nails). The systemic fungal infection of *Aspergillus fumigatus* causes pulmonary aspergillosis.
4. **Dimorphic fungi:** These can grow as filaments or as yeasts. Most fungi causing systemic infections belong to this group eg *Histoplasma capsulatum* (histoplasmosis in lungs), *Coccidioides immitis* (coccidiomycosis in pulmonary tuberculosis), *Blastomyces dermatides* (blastomycosis in pneumonitis). Another fungus in this category is *Sporothrix* (sporotrichosis in lymphatic spread).

**Classification:**

It is based on mechanism of action. Following groups have been identified:

- Inhibition of fungal cell wall synthesis (echinocandins) eg Caspofungin.
- Increasing membrane permeability (polyene group) eg Amphotericin B, Nystatin.
- Inhibition of sterol synthesis (allylamine group) eg Terbinafine.
- Inhibition of ergosterol synthesis (azole group) eg Ketoconazole and derivatives.
- Inhibition of nucleic acid synthesis eg 5-flucytosine.
- Disruption of mitotic spindle eg Griseofulvin.
- Miscellaneous topical agents eg Clioquinol, topical azoles like Miconazole.

**Drugs for Systemic Infections**

**Individual Drugs:**

**Echinocandins:** Three drugs in this category are used: Caspofungin, Micafungin and Anidulafungin.

**Mechanism of Action:**

They cause lysis of fungal cell wall by inhibiting the synthesis of 1,3-β-glucan, an essential component of the cell wall of susceptible fungi. See Fig. 3.1. Mammalian cell wall does not require 1,3-β-glucan. As a result, there is selective toxicity only to fungi and not to the host.

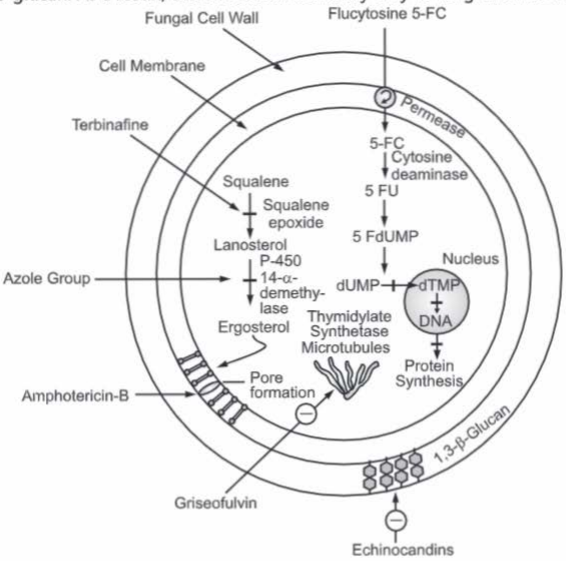



**Fig. 3.1**

**Therapeutic use:** They are used for the treatment of invasive *Aspergillus* infection and *candiasis* associated with oesophagus, intra-abdominal peritoneum, etc. Caspofungin is not orally absorbed; hence it is infused slowly. Initially, 70 mg is infused slowly followed by 50 mg/day. It is well tolerated.

**Adverse effects:** Common adverse effects include thrombophlebitis, abnormal liver functions, sensation of warmth, flushing, headache and rashes. A combination of Caspofungin with Cyclosporine can have added risk of hepatotoxicity.

**Drug interactions:** Enzyme inducers increase the clearance of Caspofungin; while Caspofungin increases the clearance of Tacrolimus.

Micafungin and Anidulafungin are more potent than Caspofungin.

**Amphotericin-B (polyene group)**

Chemically, Amphotericin-B belongs to polyene group which contains several conjugated double bonds along with a large lactone ring.

**Mechanism of Action**

Amphotericin-B binds to ergosterol, a fungal cell membrane sterol and alters the permeability of fungal cell membrane by forming pores/channels through which potassium, sodium, magnesium and hydrogen ions along with macromolecules leak out, leading to cell death. See figure 3.1. The drug has less affinity to cholesterol, which is a component of mammalian cells. Hence it causes some toxicity. Resistance to Amphotericin-B is associated with replacement of ergosterol by other sterols in fungal plasma membrane. Fungi which lack ergosterol are not susceptible to Amphotericin-B.

**Pharmacokinetics:**

It is poorly absorbed from GIT. Oral administration is effective only against fungal infections of intestine. To treat systemic fungal infections, it has to be administered by slow IV infusion. It is insoluble in water and is prepared as a colloidal suspension with sodium deoxycholate for IV infusion. It has reduced risk of nephrotoxicity. Peak antifungal activity occurs at pH 6.0-7.5. It is widely distributed in most tissues except in CSF. It is 90% bound to plasma proteins and in tissues which contain cholesterol in their membrane. Most of the drug is metabolised in liver and slowly excreted by kidney over a period of several days. Its plasma half-life is about 15 days. Dose adjustments are not needed in renal or hepatic impairment.

**Antifungal Spectrum and Therapeutic Uses:**

It is most commonly used to treat serious disseminated yeast group and some mould group of fungal infections in immunocomprised patients. It is administered systemically to treat superficial candidiasis. It remains a drug of choice in following conditions:

- Treatment of invasive aspergillosis
- Mucormycosis, an opportunistic fungal infection in lungs.
- Disseminated rapidly progressing histoplasmosis.

- Rapidly progressive coccidioidomycosis, meningeal coccidioidomycosis and paracoccidiodomycosis in immunosuppressed patients.
- Rapidly progressive blastomycosis.
- Non-AIDS cryptococcal meningitis.
- Oropharyngeal candidiasis and cutaneous candidiasis as atopical cream, lotion or ointment.
- Mycotic corneal ulcers and keratitis as topical eye drops or by direct sub-conjunctival injection.
- It is a reserved drug for Kala azar and mucocutaneous leishmaniasis.

It has no antibacterial activity. The usual therapeutic dose is 0.5-0.6 mg/Kg/day as slow IV infusion in 5% glucose for 4 hours. Amphotericin-B and Flucytosine have synergistic action on systemic candidiasis and crytptococcosis. After arresting fungal infection, antifungal azole like Miconazole can be continued.

**Adverse Effects**

- The most common adverse effect is nephrotoxicity if the total dose exceeds 5 gm.
- Hypochromic normocytic anaemia.
- Intrathecal administration may cause arachnoiditis and seizures.
- Hepatic impairment and jaundice.
- Infusion related toxicity is manifested as chills, tachypnoea, fever, vomiting and modest hypotension. Anaphylaxis is rare.

**Drug Interactions:**

Flucytosine has synergistic action with Amphotericin-B. Aminoglycosides and other nephrotoxic drugs enhance renal toxicity of Amphotericin-B. Concommitent use of diuretics should be avoided.

**Azole Group:**

These are synthetic antifungal drugs with broad spectrum fungistatic or fungicidal actions depending on drug concentration. They are divided into two groups: Imidazole and Triazole. Example of Imidazole group is Ketoconazole; while all others like Fluconazole, Itraconazole, etc belong to triazole group.

**Mechanism of Action:**

These antifungal drugs bind to the fungal cytochrome P-450-dependent 14-α-demethylase enzyme, which is responsible for demethylation of lanosterol to ergosterol. See figure 3.1. As a result, fungal cell membrane becomes leaky. They inhibit fungal respiration under aerobic conditions hence blockade of respiratory-chain electron transport is another possible mechanism.

**Antifungal Spectrum and Therapeutic Uses:**

As compared to Ketoconazole, other drugs like Itraconazole, Fluconazole, Voriconazole and Posaconazole have lesser adverse effects and are preferred. The antifungal spectrum differs within individual drugs.

**Individual Drugs:**

**Ketoconazole**

**Pharmacokinetics**

It is well absorbed from GIT if the contents are acidic. Its bioavailability is reduced in achlorhydria. Such patients should be given acidifying agents like orange juice.

It is readily distributed to most body compartments but penetration into CSF is neglible. Hence it is not useful for fungal meningitis. It is metabolised in liver and excreted in bile. Its plasma half-life is 8-10 hours but saturation of metabolism occurs slowly. Once- a- day dosing is possible. Only small amounts of drug appear in urine; hence it is not effective in treatment of fungal cystitis.

**Therapeutic Uses:**

It has restricted use in histoplasmosis and coccidioidomycosis. It is useful in silent non-CNS blastomycosis and in silent coccidioidomycosis. It is also effective against oropharyngeal candidiasis in patients of AIDS. For this purpose it is given orally. It is ineffective in the treatment of cryptococcosis, mucormycosis, aspergillosis and sporotrichosis.

**Adverse Effects:**

It causes nausea, vomiting and anorexia; but the effects can be minimised if it is taken with food. Pruritus, allergic dermatitis and reversible elevation in liver enzymes are common but hepatitis is rare. It inhibits synthesis of testosterone and estradiol which may lead to gynaecomastia in males and irregular menstrual cycle in females.

**Drug Interactions:**

It inhibits mammalian cytochrome P-450 (CYP3A4) more than fungal cytochrome P-450. Hence it causes following interactions:

- It increases serum concentration of Cisapride, Terfenadine, Astemizole and Quinidine leading to fatal ventricular fibrillation and arrthymia
- It raises plasma concentration of Warfarin, Cyclosporine, Tacrolimus and inhibitors of HMG-CoA except Pravastatin and Fluvastatin.
- Rifampicin and Phenytoin accelerate metabolism of Ketoconazole and reduce its efficacy.

It also causes following other interactions:

- $H_2$ receptor blockers (eg Ranitidine), proton pump inhibitors (eg Omeprazole) and antacids decrease absorption of Ketconazole because of decreased gastric acidity.
- It should not be used with Amphotericin-B, because depletion of membrane ergosterol reduces binding sites for Amphotericin-B.

**Fluconazole**

**Pharmacokinetics**

It does not need acidic pH for its absorption from GIT. Its plasma half-life is 27-37 hours; hence once daily dosing is possible in patients with normal renal function. About 80% of the

drug is excreted unchanged in urine, while about 10% is excreted unchanged in the faeces. Dose reduction is necessary in patients with renal insufficiency. It has least effect on hepatic microsomal enzymes. It can be given orally as well as parenterally.

**Therapeutic Uses:**

When given orally, it is effective in treatment of vulvovaginal, oropharyngeal, mucocutaneous and systemic candidiasis. A three day course of the drug is effective for urinary tract infection of candida. It is an acceptable alternative therapy for meningeal cryptococcosis, meningeal coccidioidomycosis and silent coccidioidimycosis. It has no activity against aspergillus and other filamentous fungi. Usual oral dose is 150-400 mg once daily.

**Adverse Effects:**

It is well tolerated. Nausea, vomiting, diarrhoea, headache and rashes have been reported. On prolonged therapy, increase in serum transaminase and alopecia have been observed. Since it has no effect on mammalian cytochrome P-450 enzymes, it exhibits no drug interactions of clinical significance.

- **Itraconazle**

**Pharmacokinetics:**

It requires low gastric pH for its absorption. Oral bioavailabilty is variable. When taken with food, the bioavailability is 50-60%. It is highly protein bound (99%). It has wider tissue distribution except for CSF. It is metabolised in liver and excreted in bile. It has a longer half-life of 30-35 hours. It is more specific for fungal cytochrome P-450-dependent 14-α-demethylase.

**Therapeutic Uses:**

It is most useful in long-term suppressive treatment of disseminated or chronic or pulmonary histoplasmosis in AIDS patients. It is useful in oral treatment of non-meningeal blastomycosis. It is a drug of choice for cutaneous and extra-cutaneous sporotrichosis except meningitis and has a lower relapse rate in the treatment of disseminated coccidioidomycosis and indolent paracoccidioidomycosis than Fluconazole. Itraconazole and Voriconazole are useful for invasive aspergillosis in non-immunocompromised patients. It is also useful in oropharyngeal and cutaneous candidiasis, ringworm (Tinea capitis or T corporis), fungal nail infections (T unguium) and extensive T versicolar. It is a drug of choice for treatment of pseudallescheriasis which is not responding to Amphotericin-B. Usual recommended dose is 200-400 mg once daily.

**Adverse Effects:**

Common adverse effects are headache, nausea and epigastric distress. Higher doses may cause hypokalaemia, hypertension and oedema. Serum transaminase enzyme levels may rise transiently. It does not suppress steroidogenesis. Some cases of congestive heart failure due to Itraconazole have been reported.

**Drug Interactions:**

Following drug interactions have been reported:

- Absorption of Itraconazole is impaired by antacids, $H_2$ blockers, proton pump inhibitors and drugs containing buffers.
- Itraconazole inhibits metabolism of Cisapride, Astemizole and Terfenadine resulting in increase in their plasma concentration. It may cause cardiac arrhythmia and death.
- It inhibits metabolism of Triazolam and Midazolam and prolongs hypnotic effect of these drugs.
- Rifampicin, Phenytoin and Carbamazepine accelerate metabolism of Itraconazloe and reduce its efficacy.

**Voriconazole**

**Pharmacokinetics:**

It has hig oral bioavailability (96%), low protein binding (55%) and good CSF penetration. It undergoes extensive hepatic metabolism by the enzyme CYP2C19 and only 2% of free drug is excreted in urine. Gastric acid is not necessary for its absorption. Its plasma half-life is only 6 hours. Dosage reduction is necessary in severe hepatic insufficiency but not with renal insufficiency.

**Therapeutic Uses:**

It is a drug of choice for invasive aspergillosis. It is most useful in oesophageal candidiasis. It is more active in moulds like *Fusarium and Pseudallescheria boydii* and can be used as a first line therapy. Majority of candida isolates which are resistant to Fluconazole are sensitive to Voriconazole. Recommended dose is 200 mg twice a day.

**Adverse Effects:**

Blurred vision, altered colour perception and photophobia have been reported. The effects are reversible and normalise within 1 hour. Occasionally, rashes, nausea and elevated hepatic enzymes have been reported. On prolonged use, it has been reported to cause prolongation of QTc interval.

**Drug Interactions:**

Inhibitors or inducers of CYP2C19 may increase or decrease Voriconazole plasma concentration. Rifampicin, Rifabutin, Phenytoin and Ritonavir accelerate metabolism of Voriconazole and reduce its efficacy. Metabolism of Sirolimus, Tacrolimus, Cyclosporin and Warfarin is retarded by Voriconazole leading to their significant accumulation. Grape fruit juice may increase serum Voriconazole levels.

**Posaconazole**

**Pharmacokinetics:**

It is well absorbed and even better when taken with fatty food. Plasma half-life is 25 hours. It is rapidly distributed in body tissues and is metabolised in liver. It is available as a liquid oral formulation. Usual oral dose is 400 mg BD.

**Therapeutic Uses:**

It has broad spectrum activity against candida, aspergillus infections in severely immunocompromised patients. It is equally effective in mucormycosis and zygomycosis. It is an alternative for Fluconazole-resistant oropharyngeal candidiasis.

**Adverse Effects:**

It is well tolerated but causes headache, GIT distress and occasional elevation of liver enzymes.

**Drug Interactions:**

It inhibits CYP3A4 isozymes and may increase plasma levels of Tacrolimus and Cyclosporin resulting into their toxicity.

**Flucytosine (5-FC)**

It is a fluorinated analogue of cytosine and is structurally related to anti-cancer agent 5-fluorouracil. It is devoid of anticancer activity and is a potent anti-fungal agent.

**Mechanism of Action:**

It is transported into fungal cells with the help of cytosine permease enzyme where it is converted to 5-fluorouracil by the fungal enzyme called cytosine deaminase. 5-fluorouracil is further metabolised to 5-fluorodeoxyuridine monophosphate, which is competitive inhibitor of the enzyme thymidylate synthetase and blocks the formation of thymidine monophosphate from deoxyuridine monophosphate. It inhibits fungal DNA synthesis. See figure 3.1. Mammalian cells are devoid of cytosine deaminase which prevents conversion of 5-FC to 5-fluorouracil. As a result, the drug is selectively toxic to the fungi and not to the host.

**Pharmacokinetics:**

It is well absorbed orally (90-95%). It has a plasma half-life of 3-6 hours and is excreted unchanged in the urine. Its level rises rapidly in renal impairment leading to toxicity.

**Therapeutic Uses:**

It is generally used as a part of combination therapy along with Amphotericin-B for candidiasis and cryptococcal meningitis. It is also used with Itraconazole for chromoblastomycosis. When used alone, therapeutic failure and resistance are common. When used along with Amphotericin-B, there is increase in fungal uptake of 5-FC leading to synergistic effect against candidiasis and cryptococcosis. Co-administration helps in reduction of dose of Amphotericin-B. Recommended oral dose is 50-150 mg/Kg/day in divided doses every 6 hours.

**Adverse Effects:**

Its major toxicity is bone marrow depression leading to leukopenia and thrombocytopenia. It is not tolerated by end stage HIV-infected patients with disseminated candida/cryptococcal infection. Serum levels of the drug should be closely monitored in patients with renal insufficiency. An elevation of hepatic enzymes and reversible hepatomegaly may occur in few patients. It may cause nausea, vomiting, epigastric distress and skin rash.

**Drugs for Superficial Infections (Systemic):**

The drugs from this category are used systemically not to treat systemic fungal infections but to treat superficial mycoses eg candidiasis and dermatophytoses (ringworm, tinea infection).

**Individual drugs:**

- Griseofulvin

**Pharmacokinetics:**

It is ineffective topically. It is administered orally; but its absorption from GIT is variable. Micronisation and ingestion with a fatty food improves its bioavailability. Most of the administered drug is inactivated in the liver by dealkylation. Its plasma half-life is about 24 hours. It binds to keratin precursor cells and newly synthesised keratin in the stratum corneum of skin, hair and nails making them resistant to fungal invasion.

**Mechanism of Action:**

It causes disruption of mitotic spindle and eventually arrests fungal mitosis at metaphase. See figure 3.1. It also binds to newly synthesized keratin.

**Therapeutic Uses:**

Its only use is in systemic treatment of dermatophytosis caused by *Microsporum, Trichophyton and Epidermophyton*. These are Tinea infections of skin, hair and nails. Duration of therapy depends on site of infection and is usually longer. Longer duration is needed to allow the replacement of fungal infected keratin by fresh keratin. Nail infections require longer time. Recommended dose of the micronized form is 500-1000 mg/day in two divided oral doses.

**Adverse Effects:**

Headache, nausea, vomiting, photosensitivity and peripheral neuritis are common adverse effects. Hepatotoxicity can occur in patients with acute intermittant porphyria. It is an inducer of cytochrome P450 enzymes.

**Drug Interactions:**

It can decrease effectiveness of Warfarin and oral contraceptives. It causes Disulfiram-like reaction with alcohol leading to vomiting, headache, flushing and tachycardia.

**Terbinafine:**

It is a synthetic allylamine group of antifungal agents.

**Pharmacokinetics:**

Its oral bioavailability is 50-70%. It is highly lipophilic and keratophilic resulting in high concentration in stratum corneum, sebum, hair and nails. It has a prolonged terminal half-life of 15 days due to slow release from skin, nails and adipose tissue. It has negligible effect on cytochrome P450 enzymes. Dose adjustment is needed in renal and hepatic insufficiency.

**Mechanism of Action:**

It inhibits fungal enzyme squalene epoxidase which converts squalene to lanosterol. See figure 3.1. Reduced lanosterol decreases ergosterol production which affects integrity and function of fungal cell membrane. It also decreases ergosterol biosynthesis and inhibits squalene epoxidase rather than cytochrome P450 dependent 14-α-demethylase enzyme system. It is also keratophilic and fungicidal.

**Therapeutic Uses:**

It can be used systemically in a dosage of 250 mg/day in two divided doses. It can also be used topically. Orally, it is used to treat onychomycosis of toe nail/finger nail while topically, it is used to treat Tinea infection like ringworm, athlete foot, etc. It is also useful for topical treatment of cutaneous candidiasis and pityriasis vesicolor.

**Adverse Effects:**

It causes headache, GIT upset and elevation of liver enzymes. Rarely, it may cause symptomatic hepatobiliary dysfunction.

**Topically Used Drugs:**

**Individual Drugs:**

**Nystatin:** It is polyene antifungal drug having structural similarity and mechanism of action with Amphotericin-B. It is too toxic for systemic use. It is used primarily to treat candidal infections of the mucosa, skin, GIT and vagina. It is not absorbed from skin, mucus membrane or GIT. Hence chances of toxicity are rare. When taken orally, it has bitter and foul taste.

**Topical Azoles:** The examples in this category are Clotrimazole, Miconazole, Ketoconazole, Butaconazole, Econazole, Oxyconazole, Sulconazole, Terconazole, Tioconazole and Sertaconazole.

These drugs are effective for tinea corposis, tinea pedis, tinea crutis, tinea versicolor; cutaneous, oro-pharyngeal and vulvovaginal candidiasis. Absorption is negligible and adverse effects are rare. They are available as skin ointment, cream, lotion, vaginal cream and as vaginal tablet. Shampoo from Ketoconazole is available for treating seborrheic dermatitis. Topical Azoles along with corticosteroids are available as fixed dose combinations.

**Topical Allylamines:** The examples in this category are Terbinafine, Butenafine and Naftifine. Naftifine is available as 1% cream for topical use for cutaneous dermatophytosis and candida infections. Butinafine is structurally related to Naftifine and is available as 1% cream to be applied once daily for superficial dermatophytosis (tinea infections). Terbinafine is also used as 1% cream for treatment of tinea pedis, tinea cruris, tinea corporis and tinea versicolor.

**Ciclopirox:** It is available as 1% cream and lotion for the topical treatment of dermatomycosis, cutaneous candidiasis and tinea versicolor. Higher concentration (8%) can be used for the treatment of mild to moderate onychomycosis of finger nails and toe nails. It acts by inhibiting the membrane uptake of amino acids and ions needed for fungal growth.

**Tolnaftate:** It is a synthetic antifungal drug. It distorts hyphae and mycelia growth of yeast-like fungi and moulds. It is effective in the topical treatment of dermatomycosis and tinea. Infections of palms, soles and nails are usually unresponsive to it.

**Clioquinol:** It can be used topically to treat dermatophycosis, tinea barbae, seborrhoeic dermatitis and pityriasis vesicolor. It is also useful as vaginal cream for monilial and trichomonas vaginitis. It is available as 3-8% cream.

**Benzoic acid and sodium thiosulphate:** Sodium thiosulphate is a weak fungistatic. Its 20% solution, if applied twice daily for a month is effective in pityriasis vesicolor. It is not useful in other superficial mycosis. Benzoic acid is also a weak fungistatic. It is used in combination with salicylic acid. A common preparation named Whitfield ointment contains 6% benzoic acid and 3% salicylic acid. When applied on hyperkeratotic lesion, salicylic acid helps to remove the infected tissue and promotes the penetration of benzoic acid into the fungal infected lesion.

**Preparations:**

- Ketoconazole: 200 mg tab: **Fungicide, Nizral, Funazole;** 2% cream, 2% solution: **Nizral;** 2% shampoo: **Danruf;** 2% lotion: **Hyphoral.**
- Fluconazole: 50 mg, 150 mg 200 mg tab: **Fusys, Zocon;** 50 mg, 100 mg, 150 mg, 200 mg cap, 2 mg/ml IV infusion: **Syscan.**
- Itraconazole: 100 mg cap: **Canditral, Candistat, Sporanox;** 100 mg cap, 10 mg/ml injection: **Itaspor.**
- Voriconazole: 50 mg, 200 mg tab, 200 mg/vial injection: **Vfend, Vonaz.**
- Griseofulvin: 250 mg tab: **Grisovin-FP, Walavin-FP, Grisoral.**
- Terbinafine: 250 mg tab: **Fungotek, Lamisil, Zimig, Exifine;** 1% cream: **Exifine, Fungotek.**
- Nystatin: 5 lac U, 1 lac U vaginal tab, 1 lac U/gm ointent: **Mycostatin;** 1 lac U/gm eye ointment: **Nystin.**
- Clotrimazole: 1% lotion, cream, powder: **Surfaz, Candid.**
- Econazole: 1% cream: **Ecoderm;** 150 mg vaginal tab: **Ecanol.**
- Miconazole: 2% cream: **Candistat, Micogel, Fungitop;** 2% lotion, ointment, powder: **Zole.**
- Oxyconazole: (Oxyconazole 1% + Benzoic acid 0.2%) lotion, cream: **Zoderm-E.**
- Terconazole: 0.8% vaginal cream: **Gino-Terazole.**
- Sertaconazole: 2% cream: **Onabet.**
- Butenafine: 1% cream: **Butop, Fintop.**
- Ciclopirox : 1% cream: **Olamin, Batrafen.**
- Tolnaftate: 10 mg/ml solution: **Tinaderm, Tolsol;** (Tolnaftate 10 mg + Betamethasone 0.61 mg + Gentamycin 1 mg + Iodochlorohydroxyquinone 10 mg) cream: **Quinaderm.**

## 3.4 ANTI-VIRAL DRUGS

Virus is an ultra-microscopic infectious parasite responsible for many diseases. They consist of a core genome of nucleic acid (either RNA or DNA) contained in a protein shell called capsid. In many viruses, it is surrounded by a lipoprotein membrane called envelope. See Fig. 3.2. The whole structure (genome + capsid + envelope) is called as virion, the intact virus particle.

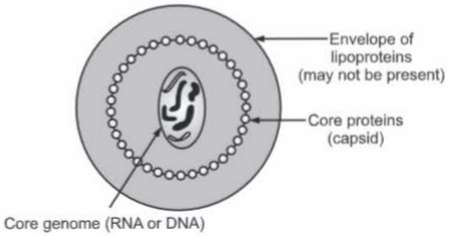



**Fig. 3.2**

A virus is active only when it is within the host cell. Hence they are called as obligate (entirely dependent on) parasites. Virus outside the host cells is inert and it canot replicate independently. They not only replicate in host cells but direct them to make new viral particles. Hence it is difficult to identify an antiviral drug which can selectively inhibit or kill virus without being toxic to host.

**Classification of Viruses:**

They are classified as DNA viruses and RNA viruses depending on which genomic material they contain.

**DNA viruses:**

Following DNA viruses are clinically important:

1. **Adeno viruses:** They are related to upper respiratory tract and eye infection.
2. **Hepadna viruses:** They cause hepatitis B.
3. **Herpes viruses:** They are further subclassified as follows:
   - **(a) Herpes Simplex Virus Type 1 (HSV 1):** It causes oral herpes, ocular herpes, viral encephalitis and herpes keratitis.
   - **(b) Herpes Simplex Virus Type 2 (HSV 2):** It causes genital herpes.
   - **(c) Varicella ZosterVirus (VZV):** It causes chicken pox, herpes zoster or shingles.
   - **(d) Cytomegalovirus (CMV):** It causes infectious mononucleosis.
   - **(e) Epstein-Barr virus (EBV):** It causes infectious mononucleosis, B-cell lymphoma.
4. **Papilloma viruses:** They cause warts.
5. **Poxviruses:** They cause small pox.
6. **Parvo viruses:** They cause erythema infectiosum, aplastic anaemia.

**RNA Viruses:**

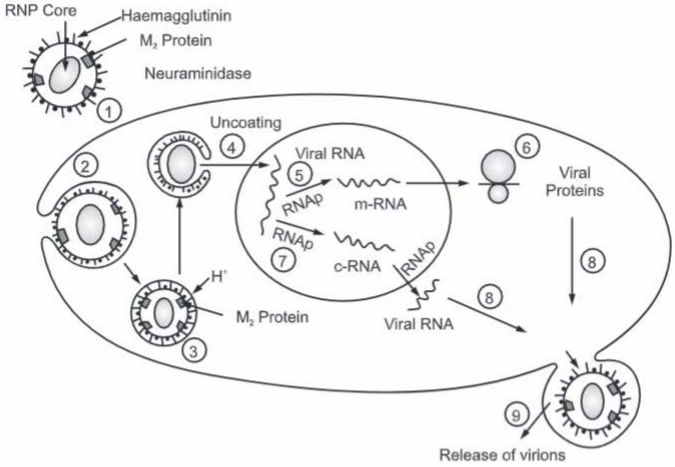
Following RNA viruses are clinically important:

1. **Picorna viruses:** They include *Poliovirus* causing polio and *Hepatovirus* causing hepatitis A.

2. **Orthomyxoviruses:** They include *Influenza virus type A, B, C, $H_1B_1$ virus*causing swine flu.
3. **Paramyxoviruses:** They include *Rubulavirus* causing mumps; *Morbilivirus* causing measles and *Respiratory syncytial virus* causing lower respiratory tract infection.
4. **Rhabdoviruses:** They cause rabies.
5. **Arboviruses:** They are arthropod borne viruses which include *Toga (alpha) virus* caisung chikungunya and encephalitis; *Flacvyvirus* causing dengue and yellow fever and *Bunyavirus* causing encephalitis.
6. **Rotavirus:** They cause gastroenteritis in children.
7. **Retrovirus:** They include *Human Immune Deficiency Virus* causing AIDS and *Human T-cell Leukaemia Virus* causing T-cell leukaemia.
8. **Arenavirus:** They cause viral meningitis, and
9. **Coronavirus:** They cause upper respiratory tract infections.

**Viral Replication:**

Figure 3.3 and 3.4 depict replication cycle of a DNA virus and RNA virus respectively. There are various steps in each cycle. They are discussed below.




Key: RNP-Ribonucleoprotein (RNA + nucleoprotein; 8 segments)
cRNA-Complementary RNA; RNAp-RNA polymerase DNAp-DNA polymerase
mRNA-Messenger RNA

**Fig. 3.3**

**Steps involved in replication of DNA viruses (Fig. 3.3)**

**Step 1:** Specific receptor sites on the DNA virus recognise corresponding surface proteins on the host cell and get attached to them.

**Step 2**: The virus then penetrates the host cell membrane by endocytosis.

**Step 3:** During penetration, if the virus has an envelope, the capsid part of the envelope merges with the host cell membrane and the genome of virus enters the interior of the cell. During the process, capsid is removed.

**Step 4:** Once the viral genome enters the cell nucleus, its DNA is transcribed into viral m-RNA by the host cell's RNA polymerase.

**Step 5:** Host cell's ribosomes then utilise the viral m-RNA for the synthesis of viral proteins and enzymes.

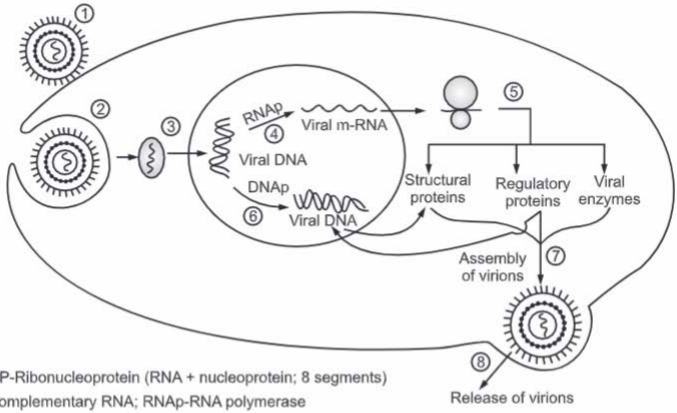
**Step 6:** During this process, the regulatory proteins are synthesised first, which in turn initiate the transcription of the early genes responsible for replication of viral DNA by viral DNA polymerase.

**Step 7:** After the DNA is replicated, the late genes are transcribed and translated to produce structural proteins required for an assembly of new virions. Following their production, the viral components are assembled to form a mature virus particle.

**Step 8:** The release of progeny virus takes place through budding of the host cell.

After these steps, the host cell is not lysed in all cases, but within certain viruses, the host cells are lysed and damaged.

**Steps involved in replication of RNA viruses (Fig. 3.4)**




Key: RNP-Ribonucleoprotein (RNA + nucleoprotein; 8 segments)
cRNA-Complementary RNA; RNAp-RNA polymerase
DNAp-DNA polymerase mRNA-Messenger RNA

**Fig. 3.4**

Most RNA viruses complete their replication in the cytoplasm without involving host cell nucleus. However, some eg influenza virus, are transcribed in the host cell nucleus. In the replication cycle of influenza (RNA) virus, the step 1 (attachment) and step 2 (endocytosis) are same as that for DNA virus. Step 3 to step 8 are different and are described below:

**Step 3:** The $M_2$ proteins (ion channels) of the virus allow an influx of $H^+$ ion into the interior of the virion which promotes dissociation of ribonucleoprotein (RNA + nucleoproteins) segments.

**Step 4:** Dissociated nucleoprotein is then released into the cytoplasm, except in the case for influenza virus where the viral genome gets entry into the host cell nucleus.

**Step 5:** Viral polymerase now synthesizes viral m-RNA from genomic viral RNA.

**Step 6:** Viral m-RNA is then translated by host cell ribosomes to synthesise structural and non-structural proteins.

**Step 7:** Replication of viral RNA can also take place via replicative form of c-RNA (complimentary RNA) using viral RNA polymerase.

**Step 8:** It involves assembly of virus particles.

**Step 9:** It involves budding and release of progeny virus.

Neuraminidase enzyme present in virions, play an important role for the release of progeny virus. The release of progeny virus usually occurs through budding and protrusion of host cell except in the case of polio virus where the host cell is damaged due to lysis.

**Antiviral drugs (non-retro viral infections):**

Viral diseases can be controlled by vaccination, use of antiviral drugs or by stimulating host defense mechanisms. Vaccines are available to prevent measles, small pox, chicken pox, rubella, mumps, poliomyelitis, yellow fever and for hepatitis B. Vaccines have only preventive role.

For an antiviral drug to be optimally active, the patient must have a competent host immune system which can eliminate or effectively halt virus replication. The chemotherapy of viral infections may involve inhibition of any one of the steps in viral attachment, uncoating, penetration, replication, growth and release of progeny virions as shown in figures 3.3 and 3.4.

**Classification:**

Antiviral drugs are classified into five major classes as mentioned below:

- DNA polymerase inhibitors.
  - Purine analogues: e.g. Acyclovir
  - Pyrimidine analogues: e.g. Idoxuridine
  - Non-nucleosides: e.g. Foscarnet
- m-RNA synthesis inhibitors: e.g. Ribavirin.
- Inhibitors of viral penetration and uncoating: e.g. Amantadine.
- Neraminidase inhibitors: e.g. Zanamivir.
- Immunomodulators : e.g. Interferons.

**Individual Classes:**

**(1) DNA Polymerase Inhibitors:**

- Acyclovir and Valacyclovir

These drugs inhibit the enzyme DNA polymerase.

**Mechanism of Action:**

It is a guanosine analogue which is converted to its active metabolite via three phosphorylation steps. The active form is Acyclovir triphosphate, which inhibits viral DNA polymerase and prevents its replication by terminating the elongation of viral DNA chain. It blocks step 6 related to DNA viruses. It has two reasons for selective toxicity:

(a) In the non-infected host cell, the phosphorylation of Acyclovir occurs to a limited extent only.

(b) Acyclovir triphosphate inhibits viral DNA polymerase 10-30 times more effectively than the host cell DNA polymerase.

**Pharmacokinetics:**

Orally administered Acyclovir has a limited bioavailability (20-30%). Hence peak plasma concentrations are sufficient only for prophylaxis or treatment of highly susceptible infections like genital herpes. About 90% of the drug is excreted unchanged in urine. In normal healthy persons the plasma half-life is 3-4 hours which increases to 20 hours in patients of renal failure.

**Antiviral Spectrum and Clinical Use:**

It is highly effective against *Herpes Simplex Virus1 (HSV-1)* which causes herpes labialis (cold sores), herpes oesophagitis, herpes keratitis, herpes encephalitis and ocular herpes; *Herpes Simplex Virus-2 (HSV-2)* which causes genital herpes and *Varicella Zoster Virus (VZV)* which produces chicken pox and shingles. It has weaker activity against *Epstein-Barr Virus (EBV)* and *Cytomegalovirus (CMV)*.

It is used orally only for HSV-1, HSV-2 and VZV infections. Parenteral Acyclovir is used in the treatment of chronic and recurrent HSV infections in immunocompromised patients, VZV infections and in herpes encephalitis. Its ointment is used for early genital herpes. Ophthalmic ointment is used for herpes keratoconjunctivitis. Usual oral dose is 400 mg TDS or 200 mg 4-5 times a day.

**Adverse Effects and Drug Interactions:**

Intravenous Acyclovir can cause phlebitis, rash, mild hypotension. Dose should be reduced in patients with renal insufficiency. Cyclosporine and other nephrotoxic drugs may increase the risk of renal toxicity, when used concurrently. Probenecid inhibits renal excretion of Acyclovir.

**Valacyclovir** is the L-valine ester (pro-drug) of Acyclovir. After oral administration, it gets rapidly converted to Acyclovir during its first-pass through intestine and liver. It is similar to Acyclovir except:

1. Bioavailability is 4-5 times more than oral Acyclovir.

2. It requires less frequent dosing.
3. It is more effective in treating herpes zoster, VZV infections and recurrent genital herpes.
4. No intravenous formulation is available.

Oral dose is 1 gm BD or TDS for 7-10 days.

**Ganciclovir and Valganciclovir:**

**Ganciclovir** is hydroxylated analogue of Acyclovir with similar mechanism of action. After conversion to triphosphate by herpes virus specific thymidine kinase, it is incorporated into viral DNA, which inhibits viral DNA polymerase and terminates its replication.

**Pharmacokinetics:**

It has poor bioavailabilty (8-10%). It is usually administered intravenously for active viral infections. Following IV administration, it shows high accumulation in vitreous humour. It is hardly metabolised and excreted unchanged in urine. Its plasma half-life is about 3-4 hours.

**Antiviral Spectrum and Clinical Use:**

It is used for treatment of serious and vision-threatening retinitis due to CMV in immunocompromised cases. It is also effective for Acyclovir-resistant HSV infections. It is used for prevention of CMV infections in organ transplant patients and in immunocompromised individuals. Ganciclovir triphosphate has 100-fold more accumulation in CMV infected cells and is preferentially incorporated in viral DNA by viral polymerase; hence it has selective efficacy in this condition. Usual dose for induction is 5 mg/Kg BD IV; maintenance dose is 5 mg/Kg/day.

**Adverse Effects and Drug Interactions:**

The most common adverse effect is myelosuppression, which may or may not be reversible. Mammalian bone marrow cells are sensitive to the drug. It has increased potential for dose-dependent neutropenia, amaemia and thrombocytopenia. Other side effects are fever, phlebitis and pain. Adjustment of doses is necessary in renal impairment.

Zidovudin can potentiate myelosuppression, when used concurrently. Cyclosporine can potentiate nephrotoxicity, when used together. Ganciclovir increases Didanosine levels whereas Probenecid increases serum levels of Ganciclovir.

**Valganciclovir** is a L-valine ester (pro-drug) of Ganciclovir. It is well absorbed from GIT and rapidly metabolised to Ganciclovir. The bioavailability of derived Ganciclovir is 60%. Its bioavailability is increased when given with food. Its mode of action, clinical uses, adverse effects and drug interactions are similar to that of Ganciclovir. Oral Valganciclovir is comparable to IV Ganciclovir for the treatment and suppression of CMV, retinitis in AIDS patients. Usual oral dose for induction is 990 mg BD, maintenance dose is 900 mg once a day.

**Famciclovir and Penciclovir:**

**Penciclovir** is a guanine nucleoside analogue with structural similarity to Acyclovir. It is less potent than Acyclovir in inhibiting viral DNA polymerase. Acyclovir –resistant HSV strains are also resistant to both Famciclovir and Penciclovir. Bioavailability of oral Penciclovir is uncertain. It is available as 1% topical cream. The active triphosphate form of Penciclovir has a longer life of 8-20 hours.

**Famciclovir** is the diacetyl ester (pro-drug) of Penciclovir. During its first pass from GIT to systemic circulation, it gets converted to Penciclovir. Boiavallability of resultant Penciclovir is about 75-80%. Its plasma half-life is 2-3 hours. It is excreted unchanged in urine. Dose adjustment is necessary in renal insufficiency.

Topical Penciclovir is used for treating herpes labialis. Famciclovir is useful for the treatment of acute localised VZV infections (shingles). It is effective like Acyclovir in treatment of HSV-1 and HSV-2 infections. Adverse effects include fatigue, GIT distress, anorexia and headache. Drug interactions are similar to Acyclovir. Usual oral dose is 500 mg TDS for 7 days.

**Vidarabine:** It is an adenine nucleoside analogue obtained from *Streptomyces antibioticus*. It inhibits viral DNA synthesis by blocking DNA polymerase. It also acts as DNA chain terminator. Viral DNA polymerase is more susceptible to Vidarabine as compared to host DNA polymerase.

Because of its poor GIT absorption, poor lipid solubility and its deamination to weakly active metabolite, it is used topically as an ophthalmic ointment. It is used for treatment of HSV keratoconjunctivitis, and superficial keratitis in patients who are not responsive to or are hypersensitive to Idoxuridine. Adverse effects are limited to lacrimation, irritation and photophobia. Concommitent use of ophthalmic steroids should be avoided, because it may spread HSV infection.

**Cidofovir:** It is an analogue of cytidine which gets converted to Cidofovir diphosphate, which inhibits viral DNA polymerase. It has poor oral bioavailability and is applied topically or given intravenously. It has plasma half-life of 2-3 hours; but its diphosphate form persists for a long time permitting once a week IV dosing. It is not metabolised significantly and is excreted unchanged in urine. Intravenously, it is administered with Probenecid. It is used for treatment and prophylaxis of CMV retinitis and HSV mucocutaneous lesions. It is also used for Acyclovir-resistant infections and for post exposure prophylaxis against small pox and for ano-genital warts. Usual IV dose for induction is 5 mg/Kg once in a week and for maintenance 5 mg/Kg every 15 days. Commonest adverse effect is nephrotoxicity. Other nephrotoxic agents like aminoglycosides, Amphotericin-B should be avoided. Foscarnet potentiates its nephrotoxicity. Other adverse effects include decrease in intra-occular pressure, uveitis and neutropenia.

**Adefovir:** It is an analogue of adenosine monophosphate. It is phosphorylated to active diphosphate derivative which competitively inhibits HBV DNA polymerase. It also gets incorporated in viral DNA and causes chain termination. Oral bioavailability is 40-60%. It is excreted unchanged in urine. Plasma half-life is 6-8 hours. It is mainly used for treatment of HBV infections and is effective even in Lamivudine-resistant strains of HBV. Its usual oral dose is 10 mg OD. Major adverse effect is nephrotoxicity. Other adverse effects include lactic acidosis and hepatomegaly. Ibuprofen increases its bioavailability by 23-25%.

**Entecavir:** It is an orally effective guanosine nucleoside analogue which competitively inhibits viral DNA polymerase and its replication. Its dose is 0.5-1 mg OD. It is used for treating chronic hepatitis B in adults with or without AIDS. It is useful in Lamivudine-resistant cases. Oral bioavailability is 100% but decreases with food; hence it should be taken on empty stomach. Its half-life is 15 hours. Adverse effects are mild like headache, fatigue, nausea and dizziness.

**Idoxuridine:** It is an iodinated derivative of deoxyuridine. Its triphosphate derivative inhibits viral DNA synthesis by blocking viral DNA polymerase. Its incorporation in viral DNA leads to chromosomal breakage and altered synthesis of viral proteins. Similar incorporation into DNA of host accounts for its toxicity. It has only topical ophthalmic use for the treatment of HSV infections of eyelid, cornea and conjunctivitis. Adverse effects include local irritation, corneal clouding, photophobia and lacrimation.

**Trifluridine:** It is a trifluoromethyl derivative of Idoxuridine. Its triphosphate derivative is incorporated in viral DNA and inhibits viral DNA polymerase. it is more potent than Idoxuridine. It inhibits cellular DNA synthesis and is cytotoxic. It is used as a topical ophthalmic solution for the treatment of keratoconjunctivitis and recurrent keratitis due to HSV-1 and HSV-2 infections. It is also effective in patients who are unresponsive to topical Idoxuridine or Vidarabine. Adverse effects include transient burning, oedema, hyperaemia and increased intra-occular pressure.

**Telbivudine:** It is a thymidine nucleoside analogue which is phosphorylated to active triphosphate. It inhibits hepatitis-B viral DNA polymerase and prevents viral replication. It is used to treat chronic hepatitis-B. Common adverse effects include elevation in creatine phosphokinase, headache, nausea and vomiting.

**Foscarnet:** It is an inorganic pyrophosphate and does not require phosphorylation for inhibiting viral DNA polymerase. It is 100 times more selective for herpes DNA polymerase than for mammalian DNA polymerase. It has a poor bioavailability; hence it is administered intravenously. It accumulates in aqueous humour and bones and is eliminated unchanged in urine. It is used for treatment of Acyclovir-resistant mucocutaneous HSV infections in AIDS patients and for CMV retinitis. Its dose is 90 mg/Kg intravenously at 12 hourly interval for induction and 90 mg/Kg/day for maintenance.

Its adverse effects include renal toxicity and electrolyte disturbances, including hypocalcaemia, hypomagnesaemia and hypokalaemia which may lead to neurological and cardiovascular disturbances. Other adverse effects include malaise, nausea, vomiting, headache, anaemia, leukopenia and liver dysfunction. Drugs like Acyclovir, Aminoglycosides, NSAIDs, Amphotericin-B, Ritonavir and Saquinavir potentiate renal toxicity of Foscarnet.

**(2) m-RNA Synthesis Inhibitors:**

**Ribavirin:** It is a synthetic analogue of guanosine with a broad spectrum activity against DNA as well as RNA viruses. It inhibits the synthesis of viral m-RNA, step 5 as shown in figure 3.4 and DNA by depleting intracellular nucleotide reserves. Its oral absorption is rapid, first-pass is extensive, still bioavailability is 65% which may increase to 75% with a fatty meal. It is also administered as aerosol. It is metabolised in liver and is excreted in urine. Plasma half-life is 9-10 hours, but the terminal half-life is 20-36 hours.

Its aerosol is used to treat influenza. It is highly effective against influenza-A and influenza-B viruses. Its oral dose is 800-1200 mg/day. It is usually combined with subcutaneous interferon. Adverse effects include worsening of respiration. It carries potential mutagenic, carcinogenic and teratogenic risk. Additional adverse effects include anaemia, hypotension and deterioration of cardiac function.

**Fomivirsen:** It is an oligonucleotide which is an anti-CMV agent. It binds to m-RNA and inhibits synthesis of immediate early proteins needed for viral replication. It has selective accumulation in retina and vitreous humour. It is injected intravenously for CMV retinitis in patients with AIDS. Adverse effects include iritis, vitreitis and increased intraocular pressure.

**(3) Inhibitors of Viral Pentration and Uncoating:** These drugs are used for treating influenza-A and B infections.

**Amantadine and Rimantadine:**

**Amantadine** is a synthetic tricyclic amine and **Rimantadine** is its α-methyl analogue. Both have similar actions more on influenza-A; and less on influenza-B virus. They inhibit viral $M_2$ protein as shown in figure 3.4 present in influenza-A viral membrane. They have no effect on viral RNA polymerase activity. Both are readily absorbed from GIT. Plasma half-life is 17-30 hours for Amantadine and 25-33 hours for Rimantadine. Amantadine is excreted unchanged (95%) in urine. Rimantadine is partly metabolised in liver; its conjugated metabolites and some free drug (25%) is excreted in urine.

Both drugs are administered orally for prevention and treatment of influenza-A. The dose for both drugs is 100 mg BD orally. They reduce duration of fever and other complaints. An additional use of Amantadine is in treating Parkinson's disease.

**Docosanol:**

It is a long chain saturated alcohol which is available as an ointment for herpes labialis. It is active against some HSV strains, CMV and some RNA viruses, eg influenza virus and paramyxovirus. It prevents entry of the virion into host cell by inhibiting the fusion between the viral envelope and the host plasma membrane. See step 1 and 2 shown in figure 3.3 and 3.4. It is used only topically as a cream.

**(4) Neuraminidase Inhibitors:**

Neuraminidase enzyme is involved in influenza virus-A and B for budding of new virus from an infected host cell. See step 8 and 9 in figure 3.4. Inhibition of neuraminidase activity prevents release of progeny virus and blocks viral spread.

**Oseltamivir and Zanamivir:**

Both drugs are neuraminidase inhibitors and are effective against various influenza strains. Orally administered **Oseltamivir** is converted to its carboxylate, which has 80% bioavailability. Its plasma half-life is 8 hours and is eliminated mainly in urine. Oral bioavailability of **Zanamivir** is only 5%. It is administered by a inhaler. Its plasma half-life is 3.5 hours and is excreted in urine.

Both drugs are used for the treatment of acute uncomplicated influenza-A (including $H_1N_1$; swine flu) or influenza-B infections. Dose of Oseltamivir is 75 mg BD orally for treatment and 75 mg OD for prevention. Dose of Zanamivir is 10 mg BD inhalation for treatment and 10 mg/day for prevention. Treatment should begin within two days of onset of symptoms. Common adverse effects for Oseltamivir are nausea, vomiting, vertigo, seizures and aggrevation of diabetes. Zanamivir causes bronchospasm, broncho secretions and nasal discomfort.

**Peramivir:** It is used for emergency treatment of hospitalised patients with $H_1N_1$ influenza infection. Its oral bioavailability is very poor and is given by intravenous route for patients showing resistance to Oseltamivir and Zanamivir.

**Other antiviral drugs:** In this category, the only drug is Palivizumab, which is a humanised monoclonal antibody directed against the highly specific antigenic site present on the cell surface of Respiratory Syncytial Virus (RSV). The dose is 15 mg/Kg intramuscularly once a month for 5 months. Adverse effects include pain at the injection site and a transient elevation in serum aminotransferase levels.

**(5) Immunomodulators:** See section 4.4 for details.

**Antiviral Drugs (Retro Viral Infections)**

Acquired Immuno Deficiency Syndrome (AIDS) is attributed to Human Immuno Deficiency Virus (HIV), which is a single stranded RNA retro virus. In retro viruses, DNA is transcripted from RNA. The word retro means reverse. It happens because of an enzyme called viral RNA-dependent-DNA polymerase. In case of HIV infection, the cell mediated immunity collapses due to continued decline in $CD4^+$-T lymphocyte cells. As a result, massive oppurtunistic infections and malignancies appear which may cause death. Thus, occurrence of AIDS is an end stage of chronic HIV infection.

**Replicative Cycle of HIV:** HIV contains surface proteins composed of knob-like glycoproteins (gp120) linked to a transmembrane stalk (gp41). These glycoproteins are antigenic and facilitate viral attachment to $CD4^+$ cells of T-lymphocytes.

HIV can infect T-lymphocytes, macrophages, Langerhans cells and dendritic cells of CNS. Various steps are involved in infection of HIV virus to host cells. The steps are indicated in Fig. 3.5.

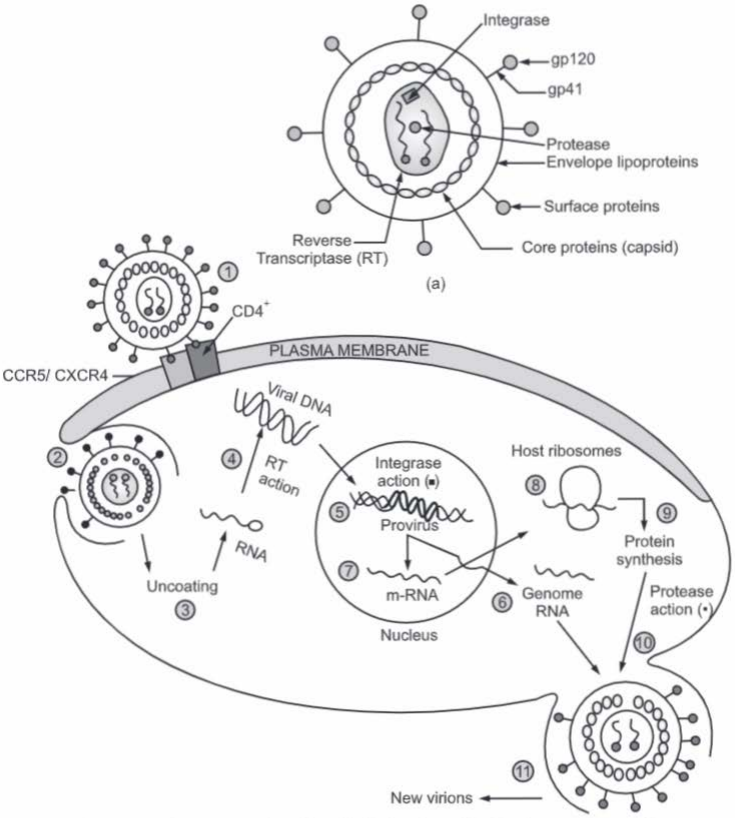



**Fig. 3.5: Various steps involved in infection of HIV virus to host cells**

**Step 1:** The surface glycoprotein, gp120 on the HIV envelope binds to $CD4^+$ and to chemokine coreceptor (CXCR4) present on T cells. In addition, gp41, causes fusion of the viral envelope with the plasma membrane of T cells.

**Step 2:** After fusion of the virus with host cell membrane, the virus enters the target cells.

**Step 3:** After entering the host cell, the virus gets uncoated.

**Step 4:** The viral reverse transcriptase (RT) synthesises DNA from viral RNA.

**Step 5:** The viral DNA enters the host cell nucleus and is integrated into the host genome, by the viral enzyme integrase, producing pro-virus.

**Step 6:** The pro-virus DNA is then transcribed into new genomic RNA.

**Step 7:** Subsequently, m-RNA is formed.

**Step 8 and 9:** The resultant m-RNA is translated into viral proteins by host ribosomes.

**Step 10:** The new virions assemble genomic RNA and polypeptides and undergo a process of maturation in which the viral protease enzyme cleaves the polypeptide into functional structural proteins and viral enzymes.

**Step 11:** The resultant mature virion then buds out from the cell membrane to infect other susceptible cells until eventually the immune response fails.

**Drug Therapy of HIV Infection:**

The replicative cycle of HIV presents many oppurtunities for targeting of antiviral drugs against HIV. However, majority of available drugs have serious adverse effects, unwelcome drug interactions and have to be taken life-long. The virus may be lying latent in the memory T cells, integrated into host genome, forming a source of potential reactivation after stopping the drug. The HIV virus has a high mutation rate, cross-resistance between the drugs; hence it is difficult to eradicate.

**Classification of Anti-HIV Drugs:**

The anti-HIV drugs are classified into following classes:

1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs): eg Zidovudine.
2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs): eg Nevirapine.
3. Nucleotide Reverse Transcriptase Inhibitors (NtRTIs): eg Tenofovir.
4. Protease Inhibitors (PIs): eg Indinavir.
5. Entry/Fusion Inhibitors: eg Enfuvirtide.
6. CCR5 Inhibitors: eg Maraviroc.
7. Integrase Inhibitors: eg Raltegravir.

**Individual Classes:**

**(1) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

The examples in this category are: Zidovudine, Stavudine, Lamivudine, Abacavir, Zalcitabine, Emtricitabine and Didanosine.

**Mechanism of Action:**

1. These drugs are converted into their triphosphate metabolites by host cell kinase enzymes. The triphosphate form competes with viral nucleoside triphosphates for their access to viral reverse transcriptase (RT) enzyme and hinders its action to produce complimentary DNA from RNA. It blocks the step 4.
2. NRTIs either lack 3'-OH group, present in nucleoside or have an azido group ($N_3$) in place of 3'-OH. See Fig. 3.6. Hence these are falsely incorporated into a growing viral DNA chain by viral RT. This results into the termination of elongation of DNA chain.

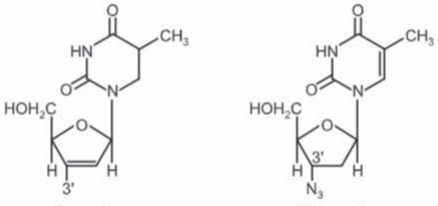



**Fig. 3.6: Structure of Stavudine and Zidovudine**

Thus these drugs block the HIV replication and consequently the infection of new cells. They do not affect already infected cells.

**Therapeutic Uses:**

These are generally used in combination with other drugs to avoid development of resistance. The multidrug therapy is called as Highly Active Anti-Retroviral Therapy (HAART). During combination, it is ensured that each contributory drug has different mechanism of action. Popular combination choices include: two NRTIs + one NNRTI or one/two PIs. The preferred drug regimens are: Zidovudine + Lamivudine + Efavirenz; or Zidovudine + Lamivudine + Lopinavir/Ritonavir. If mono therapy is used, there are chances of resistance.

**Adverse Reactions:**

Initially, toxicity is less; but at later stage when the cell-mediated immunity starts declining, the drug toxicity is more. All NRTIs cause fatal lactic acidosis, severe hepatomegaly and hepatic steatosis. Women, obese persons and alcoholics are more prone to toxicity. If toxicity is severe, the drug should be withdrawn.

**Individual Drugs**

**Zidovudine:**

It is a thymidine analogue contining azido ($N_3$) group. See figure 3.6. It provides an effective treatment of HIV-1, HIV-2 and human T-cell lymphotrophic virus (HTLV-I and II). It is also used for post exposure prophylaxis of health care workers. Its oral bioavailability is 60-65% and plasma half-life is 1-3 hours. As a preventive measure, it significantly reduces the incidence of neonatal HIV infection when the HIV-infected mother is given the drug in a dose of 100 mg 5 times a day after fourteen weeks of gestation until birth. The usual recommended dose is 200 mg TDS or 300 mg BD orally. It is used in combination with Lamivudine or with Lamivudine + Abacavir.

**Adverse effects** include headache, nausea, vomiting, anorexia, fatigue, insomnia, myopathy and myositis. Prolonged use can lead to bone marrow toxicity, anaemia and neutropenia which may need reduction in dosage or even discontinuation.

Concurrent use of drugs like Interferon-α, Cotrimoxazole, Dapsone, Foscarnet, Ganciclovir and Valganciclovir should be avoided. Zidovudine should not be combined with Ribaverin or Stavudine. Nelfinavir decreases plasma levels while Probenecid, Fluconazole and Lamivudine increase plasma levels of Zidovudine.

**Stavudine:**

It is a thymidine analogue which is devoid of hydroxyl group at 3-position. See Fig. 3.6. It is used for the therapy of HIV infections as a part of multidrug regimen (Stavudine + Lamivudine) as well as for post exposure prophylaxis. Its oral bioavailability is 85-90% and plasma half-life is 1-2 hours. The recommended adult dose is 30-40 mg BD.

Peripheral neuropathy is dose dependent. Dose adjustment is necessary for patients with renal insufficiency and peripheral neuropathy. Other adverse effects are: pancreatitis, joint pain, headache, diarrhoea, skin rash, vomiting, stomatitis, insomnia and anorexia. Lactic acidosis is more frequent with Stavudine. Concurrent administration of drugs like Didanosine, Zalcitabine and Isoniazid should be avoided. It should not be administered with Zidovudine.

**Lamivudine:**

It is a cytosine analogue and is devoid of hydroxyl group at 3-position. It is active against HIV-1, HIV-2 and hepatitis B virus. It is used in combination with other anti-retroviral drugs. It is used for post exposure prophylaxis. The combination of Zidovudine + Lamivudine enhances $CD4^+$ counts. It has oral bioavailability of 85-90% and plasma half-life of 5-7 hours. It is well tolerated.

The usual adult dose is 150 mg BD for HIV infection and 100 mg/day for hepatitis B infection. Most common adverse effects are nausea, headache, fatigue and insomnia. There is increased risk of pancreatitis in children. Dose adjustment is necessary in patients with renal insufficiency. Lamivudine and Zalcitabine inactivate each other by inhibiting each other's phosphorylation. Cotrimoxazole inhibits renal elimination of Lamivudine.

**Abacavir:**

It is a guanosine analogue devoid of hydroxyl group at 3-position. It is effective against HIV-1 infection in adults and children as well as for post exposure prophylaxis. It is used in combination with Zidovudine + Lamivudine. The usual adult dose is 300 mg BD. Its oral bioavailability is 80-85% and plasma half-life is 1.5 hours.

The adverse effects include generalised hypersensitivity reactions. These are rare but fatal. If hypersensitivity occurs, rechallenge must be avoided. Other adverse effects are headache, nausea, vomiting, fatigue, skin rash and increased myocardial infarction. It is partly metabolised by alcohol dehydrogenase; hence concurrent intake of alcohol may increase plasma levels of Abacavir.

**Zalcitabine:**

It is a cytidine analogue devoid of hydroxyl group at 3-position. It is active against HIV-1, HIV-2 and hepatitis B virus. It is administered in combination with Zidovudine and a protease inhibitor. It is suitable for patients who are intolerant or resistant to Zidovudine. The usual adult dose is 0.75 mg TDS. Its oral bioavailability is 85% and plasma half-life is 2 hours.

Peripheral neuropathy is major adverse reaction. Stomatitis, oesophageal ulceration, GIT distress, headache, malaise and oedema of lower limb are other adverse effects. Its use is contraindicated in pancreatitis, hepatitis and alcohol abuse. It should not be administered with food or antacid. Concurrent use of neuropathic drugs like Didanosine, Stavudine and Isoniazid should be avoided. Its use has been discontinued due to adverse effect profile.

**Emtricitabine:**

It is a cytosine analogue related to Lamivudine. It is used in combination with a protease inhibitor and/or a NNRTI for treatment of HIV infection in adults. A usual combination is Emtricitabine + Tenofovir + Efavirenz or Emtricitabine + Tenofovir. The usual adult dose is 200 mg orally once daily. Oral bioavailability is 93% and plasma half-life is 10 hours.

It is best tolerated and least toxic. Prolonged use can cause hyperpigmentation of skin. Hepatotoxicity and pancreatitis may result if used with a hepatotoxic drug. Dose adjustment is needed in patients with renal insufficiency.

**Didanosine:**

It is an adenosine analogue devoid of hydroxyl group at 3-position. It is active against HIV-1, HIV-2 and HTLV-I. Along with other related drugs, it is used to treat HIV infection and for post exposure prophylaxis. The usual adult dose is 250 mg BD, 30 minutes before or two hours after meal. Oral bioavailability is 42% and plasma half-life is 1.5 hours.

Its bioavailability is decreased with food, tetracyclines and fluoroquinolones. Major adverse effects include diarrhoea, peripheral neuropathy, hyperuraecemia, pancreatitis and optical neuritis. It is contraindicated in patients of gout, pancreatitis, peripheral neuropathy and patients with visual problems. Zalcitabine with Didanosine increases risk of peripheral neuropathy; while Stavudine with Didanosine increases risk of pancreatitis as well as peripheral neuropathy. Ganciclovir and Valganciclovir increase blood levels of Didanosine.

**(2) Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

The examples in this category are: Nevirapine, Efavirenz, Delavirdine and Etravirine.

**Mechanism of Action:**

NNRTIs do not require activation by phosphorylation. They bind directly to the catalytic site of viral reverse transcriptase causing enzyme inactivation and inhibition of cDNA synthesis. It blocks step 4 as shown in figure 3.5. If used alone, resistance develops due to mutations in reverse transcriptase. Hence monotherapy is not recommended. Cross resistance is noticed between different NNRTIs; but not between NNRTIs and NRTIs or between NNRTIs and protease inhibitors.

**Therapeutic Uses:**

They are active against HIV-1 reverse transcriptase only. Their use with NRTIs or protease inhibitors leads to synergistic effects due to sequential blockade at two different steps.

**Adverse Effects:**

They include skin rashes along with Stevens-Johnson syndrome. They may cause elevation in levels of liver enzymes.

**Drug interactions and contraindications**

Drug interactions due to induction or inhibition of cytochrome P450 enzymes are observed. Since protease inhibitors are also metabolised by cytochrome P450 enzymes, NNRTIs may either increase or decrease their plasma levels. NNRTIs should be used with caution in patients with hepatic disease.

**Individual Drugs:**

**Nevirapine:**

It is used for treatment of HIV infection in adults and children as a component of multidrug therapy. The recommended oral adult dose is 200 mg BD. It is useful in preventing vertical transmission of HIV (from mother to new born), if administered at the onset of labour. A single 2 mg/Kg oral dose is to be given to the neonate within three days after birth. Oral bioavailability is 95% and plasma half-life is 25-30 hours.

Adverse effects include life-threatening skin rashes including Stevens-Johnson syndrome and fulminant hepatitis with fever, within first 6 weeks of therapy. Monitoring of liver function is necessary. Other adverse effects include headache, nausea, diarrhoea and dizziness.

It is a moderate inducer of CYP3A4 and may increase its own clearance. It decreases plasma levels of drugs like Amprenavir, Indinavir, Lopinavir and Saquinavir; azole group of antifungal drugs (eg Miconazole) and Ethinylestradiol-based oral contraceptives. Enzyme inducers like Rifampicin may decrease plasma levels of Nevirapine.

**Efavirenz:**

It is used to treat HIV-1 infections in adults and children. It is also used as post-operative prophylaxis. The recommended oral daily dose is 600 mg OD. It should not be taken with fatty meals. Oral bioavailability is 50% and plasma half-life is 50 hours.

Principle adverse effects involve CNS: dizziness, nightmares, insomnia, headache and euphoria which disappear on discontinuation. Other adverse effects include skin rash, nausea, vomiting, diarrhoea, elevated liver enzymes and serum cholesterol levels. It should be avoided during pregnancy.

It is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. It is also a self-inducer. Concurrent use of Cisapride, Midazolam, Triazolam and ergot alkaloids may result in life-threatening emergencies. It increases plasma levels of protease inhibitors like Saquinavir. Phenobarbital, Rifampicin and herbal preparations like St. John's wort may decrease plasma levels of Efavirenz.

**Delavirdine:**

It is used for the treatment of HIV-1 infection in adults as a part of combination therapy. The usual adult dose is 400 mg TDS. Oral bioavailability is 85% and plasma half-life is 5-6 hours. Its use is declined because of three times dosing.

Main adverse effects include skin rash and pruritus which resolves on continuaton of therapy. Other adverse effects include diarrhoea, headache, nausea, vomiting and elevated hepatic enzymes.

Antacids reduce its bioavailability. It is metabolised by and inhibits CYP3A4 and thus it increases plasma concentration of protease inhibitors like Amprenavir, Indinavir, Lopinavir, Ritonavir and Saquinavir. Dose reduction of these drugs should be considered when administered concurrently. Plasma levels of Telavirdine are reduced by enzyme inducers like Phenytoin, Phenobarbitone, Carbamazepine and Rifampicin. It should be avoided during pregnancy.

**Etravirine:**

In an oral dose of 200 mg BD, it is indicated for use in combination with atleast two additional antiretroviral drugs for the treatment of HIV infection, resistant to other NNRTIs. Food increases its bioavailability; hence it should be administered following meal. Adverse effects include nausea and skin rash. It is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19. It should not be used along with Carbamazepine, Phenytoin, protease inhibitors, other NNRTIs, Ketoconazole, St. John wort and Rifampicin.

**(3) Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)**

**Tenofovir:**

It is available as Tenofovir disoproxil fumarate (a prodrug). It is an analogue of adenosine-5′-monophosphate. It is first hydrolysed in liver to Tenofovir, which is phosphorylated to Tenofovir diphosphate. The diphosphate salt competitively inhibits HIV reverse transcriptase and causes termination of chain elongation after getting incorporated into viral DNA. It blocks step 4 as shown in figure 3.5. It is used along with other anti-HIV drugs in the treatment of HIV. The adult daily dose is 300 mg once daily after food. Its oral bioavailability is 25% which increases to 40% after meals. Plasma half-life is 17 hours.

It is well tolerated. It causes adverse effects like nausea, vomiting and diarrhoea. It may also cause hepatomegaly, pancreatitis and lactic acidosis. It increases plasma levels of Didanosine leading to toxic effects like pancreatitis, hepatotoxicity and lactic acidosis. It decreases serum concentration of Atazanavir.

**(4) Protease Inhibitors (PIs):**

The examples in this category are Saquinavir, Indinavir, Nelfinavir, Amprenavir, Fosamprenavir, Ritonavir, Lopinavir, Atazanavir, Tipranavir and Darunavir.

**Mechanism of Action:**

The protease inhibitors (PIs) competitively inhibit the viral protease enzyme and prevent cleavage of polyproteins necessary for production of virions. This results in the production of immature, non-infectious virions. See step 10 of figure 3.5. This isoform of protease is not present in the host. Thus PIs are better option for therapeutic intervention.

**Therapeutic Uses:**

Combination therapy with PIs and other antiretroviral drugs significantly improve the clinical efficacy by blocking IHV replication at different stages in the intracellular life cycle. These agents are active against HIV-1 and HIV-2 infection. Cross resistance between Indinavir and Ritonavir can occur; but it has not been observed with PIs.

**Adverse Effects:**

These include diarrhoea, nausea and abdominal discomfort. In addition, PIs can produce hyperglycaemia, fat redistribution and hyperlipidaemia. They have risk potential for increased bleeding especially in haemophilic patients.

**Drug Interactions:**

PIs are competitive inhibitors of drugs metabolised by CYP3A4 family. As a result, plasma concentration of some drugs may increase leading to life-threatening toxicity. Related drug and effect of interaction is as follows: Cisapride (arrhtymia), Ergot alkaloids (vasospasm), Statins (rhabdomyolysis), Midazolam and Triazolam (respiratory depression).

Benzodiazepines are contraindicated with PIs. Enzyme inducers like Phenytoin, Phenobarbitone, Carbamazepine, Dexamethasone and Rifampicin may diffuse plasma levels of PIs. Drugs like Clarithromycin, Itraconazole and Ketoconazole may increase plasma levels of PIs. St. John's wort antagonises the antiviral actions of PIs.

**Common drug combinations**

- Indinavir + Zidovudine + Lamivudine.
- Nelfinavir + Zidovudine + Didanosine.
- Saquinavir + Zidovudine + Zalcitabine.
- Ritonavir + Lopinavir + Stavudine + Lamivudine.
- Ritonavir + Indinavir + Stavudine + Didanosine.

**Individual Drugs**

**Saquinavir:**

It is formulated as either a hard gel capsule/tablet or as a soft gel capsule. Oral bioavailability of these formulations is 4% and 13% respectively. Fatty meal enhances its bioavailability. Maximum bioavailability is obtained when combined with low doses of Ritonavir. Plasma half-life is 8 hours. Usual dose is 600 mg TDS orally, 2 hours after full meal. The combination of Saquinavir 1000 mg with Ritonavir 100 mg, when given twice a day, exhibits improved antiviral action and reduction in GIT adverse effects. Ritonavir increases bioavailability of Saquinavir by inhibiting its first-pass metabolism.

**Fosamprenavir:**

It is a prodrug of Amprenavir and has an advantage of better bioavailability (80%). It is suitable for Paediatric purpose also. Its usual oral dose is 700 mg with Ritonavir 100 mg twice a day. It should be avoided in patients of hepatic insufficiency. Antacids decrease its absorption.

**Indinavir:**

The recommended adult oral dose is 800 mg TDS or BD along with 100 mg BD of Ritonavir. Oral bioavailability is 65%. Food decreases its bioavailability. Plasma half-life is 1-2 hours. The adverse effects include nephrolithiasis, urolithiasis and renal insufficiency. Hence large intake of water is recommended. In addition, it causes reversible hyperbilirubinaemia, alopecia, anaemia and paronychia (nail infection).

**Nelfinavir:**

It is the most commonly used drug with low toxicity profile. Its usual adult dose is 750 mg BD. Its plasma half-life is 5 hours. Food increases its bioavailability. Common adverse effects include diarrhoea and flatulence, which resolve after continued use. It need not be combined with Ritonavir, because it is not metabolised by CYP3A4.

**Ritonavir:**

It is usually given along with Lopinavir. In low doses, it is used to increase effectiveness of other PIs like Saquinavir, Fosamprenavir and Indinavir. Its usual adult oral dose is 600 mg BD. Its oral bioavailability is 75%. Food increases its bioavailability. Its plasma half-life is 3-5 hours. It is rarely used as a single drug. It is used in low doses (100 mg BD) as a pharmacokinetic booster along with other PIs. It is a potent inhibitor of CYP3A4. It increases plasma concentration of other PIs leading to improved viral suppression.

Adverse effects include altered taste, anorexia, peripheral paraesthesias, elevated triglycerides and hepatic transaminases. It should not be given along with Amidarone, Bepridil, Propafenone, Quinidine or Pimozide; these drugs are metabolised by CYP3A4. Coadministration with Ritonavir can increase concentration of these drugs leading to toxicity.

**Lopinavir + Ritonavir:**

It is a fixed dose combination used for treatment of HIV-1 and HIV-2 infections. It is available as 4:1 ratio of Lopinavir (400 mg BD) along with Ritonavir 100 mg BD. It is given twice daily with food. This combination is not only synergistic but has lesser side effects than either drug alone. Increased doses of the combination are required if coadministered with Efavirenz or Nevirapin, which induce metabolism of Lopinavir.

**Atazanavir:**

It is active against HIV-1 and HIV-2. It has oral bioavailability of 75% which is further enhanced by food. Its absorption is acid-dependent. Hence histamine $H_2$ blockers like Ranitidine and proton pump inhibitors like Omeprazole decrease its absorption. The recommended oral adult dose is 400 mg daily. Plasma half-life is 7 hours. A combination of Atazanavir with low dose of Ritonavir is as effective as Lopinavir + Ritonavir combination.

Adverse effects include nausea, diarrhoea, reversible hyperbilirubinaemia, hyperglycaemia and hypercholesterolaemia. It has no effect on lipid profile. Efavirenz decreases plasma levels of Atazanavir.

**Darunavir:**

It is used for treatment of patients who are unresponsive due to HIV resistant mutants. It is to be coadministered with Ritonavir (600 mg Darunavir BD + 100 mg Ritonavir). It may show sensitivity reactions. Lopinavir and Saquinavir decrease, while Indinavir increases plasma levels of Darunavir.

**Tipranavir:**

It is used when patients are unresponsive to other PIs. It is coadministered with Ritonavir to increase its bioavailability. It is used as a combination with 500 mg Tipranavir and 200 mg

Ritonavir, twice daily. Food increases its bioavailability. Antacids decrease its absorption. It may show sensitivity reactions. Hepatotoxicity is the major adverse effect.

**(5) Entry/Fusion Inhibitors**

**Enfuvirtide:**

It is a polypeptide. It binds to gp41 sub-unit of viral envelope glycoproteins and prevent entry of HIV-1 into $CD4^+$ cells by interfering with the fusion of viral and cellular membrane. See step 2 in figure 3.5. Its usual adult dose is 90 mg BD given subcutaneously. Its metabolism does not involve cytochrome P450 enzyme system. Its elimination half-life is 3-4 hours. It is used with other antiretroviral drugs for the treatment of advanced HIV-1 infections in patients with viral resistance.

Adverse effects include local reaction at the injection site, skin rash, eosinophilia and pneumonia like manifestations.

**(6) Chemokine Receptors-5 (CCR5 Inhibitors)**

**Maraviroc:**

It binds to CCR-5 receptor present on CD4 cell membrane and prevents the entry of virus into the host cell. It prevents interaction of viral gp120 with CCR-5 coreceptor. See step 1 of figure 3.5. It is used with other antiretroviral virals in resistant adult patients infected with HIV. Its dosage depends on concomitant drug as mentioned below:

- When used with enzyme inducers like Phenytoin, Carbamazepine, Rifampicin, St John wort, Efavirenz and Etravirine, it is used in a dose of 600 mg BD.
- When used with enzyme inhibitors like Delavirdine, Ketoconazole, Itroconazole and Clarithromycin, it is used in a dose of 150 mg BD orally.
- Normally and with other drugs like Ritonavir + Lopinavir/Tipranavir, Nevirapine, Enfuvirtid and NRTIs, it is administered 300 mg BD orally.

**(7) Intergrase Inhibitors**

**Raltegravir:**

It inhibits the viral enzyme integrase, thereby preventing insertion of viral DNA into chromosomes of the host cells. See step 5 of figure 3.5. It halts replication of viruses. It is used along with other anti-HIV drugs, in treatment of HIV resistant patients. It is not metabolised by cytochrome P450 system. However, Rifampicin decreases levels of Raltegravir. Antacids and iron bind to integrase; hence their dosing should be separated by two hours. Usual adult oral dose is 400 mg BD. Adverse effects include nausea, diarrhoea, fever, headache and myopathy.

**Preparations:**

- Acyclovir: 200 mg, 400 mg 800 mg tab, 3% eye ointment, 5% skin ointment: **Acivir, Ocuvir;** 200 mg, 400 mg, 800 mg tab, 400 mg/5 ml suspension, 250 mg/10 ml vial for injection, 3% eye ointment: **Zovirax.**
- Valacyclovir: 500 mg, 1000 mg tab: **Nalcivir.**

- Ganciclovir: 500 mg cap, 500 mg/vial injection: **Gavir;** 250 mg, 500 mg cap: **Ganguard.**
- Famciclovir: 250 mg, 500 mg tab: **Virovir, Microvir, Famtrex.**
- Adefovir Dipivoxil: 10 mg tab: **Adesera, Adfovir, Adheb.**
- Idoxuridine: 0.1% eye drops and ointment: **Toxil.**
- Ribavarin: 100 mg, 200 mg tab, 50 ml/5 ml syrup: **Virazide, Ribavin.**
- Oseltemivir: 75 mg cap, 12 mg/ml suspension: **Tamiflu;** 75 mg cap: **Fluvir.**
- Zanamivir: 5 mg blisters for inhalation: **Relenza.**
- Zidovudine: 100 mg cap, 300 mg tab, 50 mg/5 ml syrup: **Zidovir;** 100 mg, 300 mg tab: **Viro-Z;** 100 mg cap, 300 mg tab: **Zidomax;** (Zidovudine 300 mg + Lamivudine 150 mg + Efavirenz 600 mg) kit: **Lazid-E.**
- Stavudine: 30 mg, 40 mg cap: **Stavir;** (Stavudine 40 mg + Lamivudine 150 mg) tab/cap: **Emduo-40, Stv-plus;** (Stavudine 40 mg + Lamivudine 150 mg + Nevirapine 200 mg) tab/kit: **Stv-Com, Emduo-E 40.**
- Lamivudine: 100 mg, 150 mg tab: **Virolam, Heptavir, Lami;** 100 mg, 150 mg tab, 50 mg/5 ml syrup: **Lamivir; (**Lamivudine 150 mg + Stavudine 30/40 mg) tab: **Lamivir-S;** (Lamivudine 150 mg + Zidovudine 300 mg): **Duovir;** (Lamivudine 150 mg 2 tabs + Stavudine 30/40 mg 1 tab + Efavirenz 600 mg 1 tab) kit: **Virolis-E.**
- Abacavir: 300 mg tab: **Abavir, Abamune, Virol.**
- Emtricitabine: (Emtricitabine 200 mg + Tenofovir 300 mg) tab: **Tenof-EM;** (Emtricitabine 200 mg + Tenofovir 300 mg + Efavirenz 600 mg) tab: **Trustiva.**
- Didanosine: 250 mg, 400 mg cap: **Virosine-DR, Dinex-EC, Dinosin-EP;** (Didanosine 250/400 mg + Lamivudine 300 mg + Efvirenz 600 mg) kit: **Retrodel-kit.**
- Nevirapine: 200 mg tab: **Nev, Neve, Nevimune, Nevipan.**
- Efavirenz: 200 mg, 600 mg cap: **EF;** 200 mg, 600 mg cap: **Efcure, Efferven.**
- Tenofovir Disoproxil fumarate: 300 mg tab: **Tavin, Tenof, Tentide;** (Tenofovir 300 mg + Entricitabine 200 mg + Efavirenz 600 mg) tab: **Vonavir, Trustiva.**
- Saquinavir: 200 mg cap: **Saquin.**
- Indinavir: 400 mg cap: **Virodin, Indivir, Indivan, Ind.**
- Nelfinavir: 250 mg tab: **Nel, Nelvir;** 625 mg tab: **Nelfin.**
- Ritonavir: 100 mg cap: **Empetus, Ritomax, Ritovir.**
- Lopinavir + Ritonavir: (Lopinavir 200 mg + Ritonavir 100 mg) tab/cap: **Emletra, Lopimune, Ritocom.**
- Atazanavir: 100 mg, 150 mg, 200 mg, 300 mg cap: **Atazor.**

## 3.5 ANTHELMINTICS

The helminths (worms) are macroscopic, multicellular organisms having their own digestive, excretory, reproductive and nervous system. They are either nemathelminths (round bodied worms) or platyhelminths (flat bodied worms).

Nemathelminths include Nematodes like

- Roundworms (*Ascaris lumbricoides*),
- Hookworms (*Necator americanus or Ancylostoma duodenale*)
- Whipworms (*Trichuris trichiura*)
- Threadworms (*Strongyloides stercoralis*)
- Pinworms (*Enterobius vermicularis*)
- Filarias (*Wuchereria bancrofti or Brugia malayi*)
- Onchocerciasis (*Onchocerca volvulus*)
- Guinea worms (*Dracunculus medinensis*)

Platyhelminths are of two types: Trematodes (flukes) and Cestodes (tapeworms).

Trematodes include following flukes:

- Blood flukes (schistosomiasis or bilharziasis)
- Liver flukes (clonorchiasis)
- Intestinal flukes (fasciolopsiasis) and
- Lung flukes (paragonimiasis)

Cestodes include following tapeworms:

- Beef tapeworm (*Taenia saginata*)
- Pork tapeworm (Taenia solium)
- Fish tapeworm (*Diphyllobothrium latum*) and
- Dwarf tapeworm (*Hymenolepis nana*)

The drugs which are used to get rid of helminths/worms are called as anthelmintic drugs. They may serve as either vermicide (kill) or vermifuge (expel) to the infesting helminth. Anthelminthics attack the parasite cells and not to mammalian cells. Thus they have selective toxicity only to helminths.

Most of the nematodes (roundworms, hookworms, whipworms, pinworms and threadworms) are found in intestine where they attach to the mucosa and feed on host blood and tissue fluid. Trematodes (flukes) are hermaphroditic non-segmented flattened helminths. The larvae are acquired either through ingestion of food (vegetables or fish) or through skin penetration. Cestodes are ribbon-shaped parasitic worms. They are mainly intestinal parasites and few of them invade other tissues in the larval stage.

**Mechanism of Action:**

The mechanisms are different for each type of helminth. In addition, there are some broad spectrum Anthelmintics with common mechanism of action.

**Against Nematodes:**

The locomotor muscles of nematodes have both cholinergic and GABAergic innervations and their neuromuscular junction have both excitatory cholinergic-nicotinic ($N_N$) and inhibitory GABAergic receptors.

Pyrantel pamoate and Livamisol are $N_N$ receptor agonists and also cause release of acetyl choline by inhibition of enzyme acetyl cholinesterase.

GABAergic neurotransmission in humans is primarily in CNS and not in periphery. Anthelmintic drugs cannot cross BBB and act peripherally. Piperazine is a GABA receptor agonist and activates GABA-gated $Cl^-$ channel in nematode muscles. Evermectin acts on specific glutamate-gated $Cl^-$ channels which are also inhibitory. They are found on pharyngeal muscles of nematodes. Diethylcarbamazine alters the microfilarial membrane surface in such a way that they are phagocytosed by monocytes. Doxycycline eradicates *Wolbachia*, an intracellular bacterium which is responsible for oogenesis and reproductive ability of adult female filarial parasite.

**Against Trematodes:**

Metrifonate is an organophosphorous compound and its active metabolite, Dichlorvos, inactivates acetyl cholinesterase and potentiates neuromuscular blockade of *Cystosoma hematobium*.

Oxamniquine intercalates in the parasitic DNA and causes death of cystosome by blocking its nucleic acid and protein synthesis. Bithionol uncouples parasite-specific oxidative phosphorylation. By blocking ATP synthesis, it inhibits the energy derived by the helminth from anaerobic metabolism.

**Against Cestodes:**

Niclosomide uncouples oxidative phosphorylation in adult cestode. It inhibits anaerobic incorporation of inorganic phosphates into ATP, which is detrimental to the parasites.

**Against Trematodes and Cestodes:**

Praziquantal causes influx of $Ca^{++}$ from endogenous stores of cestodes resulting in intense contractions and subsequent expulsion of the worm from the GIT.

**Broad Spectrum Anthelmintics:**

Benzimidazoles are broad spectrum anthelmintics. They include Thiabendazole, Mebendazole, Albendazole and Triclabendazole. Cytoskeletal structures of helminths include microfilaments, microtubules and β-tubulins. β-tubulin dimers are continuously polymerised from one end and then depolymerised at the other end of the microtubules. Benzimidazoles bind to β-tubulins and prevent their assembly leading to selective and irreversible inhibition of glucose uptake by these organisms. The end result is depletion of glycogen stores, reduced formation of ATP, disruption of metabolic pathway and ultimately death of parasite. They do not affect the host adversely.

**Individual Drugs:**

Table 3.2 summarises major helminth infections and drugs of first and second choice.

**Table 3.2: Choice of a drug for helminth infections**

| Sr. No. | Worm Infestation | Drug of Choice |
|---|---|---|
| | **NEMATODES** | |
| 1. | *Ascaris lumbricoides* (roundworms) | Mebendazole, Albendazole, Pyrantel pamoate |
| 2. | *Necator americanus* (hookworms) | Mebendazole, Albendazole, Pyrantel pamoate |
| 3. | *Ancylostoma duodenale* (hookworms) | Mebendazole, Albendazole, Pyrantel pamoate |
| 4. | *Trichuris trichiura* (whipworm) | Mebendazole, Albendazole |
| 5. | *Trichinella spiralis* (trichinosis) | Mebendazole, Albendazole |
| 6. | *Enterobius vermicularis* (pinworm) | Mebendazole, Pyrantel pamoate |
| 7. | *Strongyloides stercoralis* (threadworm) | Ivermectin |
| 8. | *Wichereria bancrofti* (filaria) | Diethylcarbamazine |
| 9. | *Brugia malayi* (filaria) | Diethylcarbamazine |
| 10. | *Onchocera volvulus* (onchocerciasis) | Ivermectin |
| 11. | *Dracunculus medinensis* (guinea worm) | Metronidazole |
| 12. | Cutaneous larva migrans (creeping eruption) | Albendazole, Ivermectin |
| 13. | Visceral larva migrans | Albendazole |
| 14. | Intestinal capillariasis | Albendazole |
| | **TREMATODES (FLUKES)** | |
| 1. | *Schistosoma haematobium* (bilharziasis) | Praziquantel |
| 2. | *Schistosoma mansoni* (blood flukes) | Praziquantel |
| 3. | *Schistosoma gaponicum* (blood flukes) | Praziquantel |
| 4. | *Clonarchis sinensis* (liver fluke) | Praziquantel |
| 5. | *Fasciola hepatica* (sheep liver fluke) | Bithionol, Triciabendazole |
| 6. | *Paragonimus skrjabini* (lung fluke) | Triciabendazole, Praziquantel |

*... (Contd.)*

| Sr. No. | Worm Infestation | Drug of Choice |
|---|---|---|
| | **CESTODES (TAPEWORMS)** | |
| 1. | *Taenia saginata* (beef tapeworm) | Praziquantel, Niclosamide |
| 2. | *Diphyllobothrium latum* (fish tapeworm) | Praziquantel, Niclosamide |
| 3. | *Taenia solium* (pork tapeworm) | Praziquantel, Niclosamide |
| 4. | *Hymenalepis nana* (dwarf tapeworm) | Praziquantel |
| 5. | Cysticercosis | Albendazole |
| 6. | Hydatid disease | Albendazole |

**Benzemidazoles:**

They are an important category of drugs in treating various helminth infections. Out of the four drugs mentioned below, Albendazole and Mebendazole have a broader range of anthelmintic activity while Thiabendazole and Triclabendazole have a restricted use.

**Albendazole**

**Pharmacokinetics:**

Its oral absorption is variable. Fatty meals increase its absorption. It is rapidly metabolised in liver to an active sulphoxide metabolite which has a wide distribution in different tissues, bile, CSF, hydatid, cysts. Its elimination half-life is 8-12 hours.

**Clinical Uses:**

It is a broad spectrum anthelmintic, particularly useful against intestinal nematodes and cestodes as well as against liver flukes (a trematode).

It is a drug of choice for various nematodes like roundworm, whipworm and hookworms. See table 3.2. The recommended for adults and children above two years, is 400 mg orally as a single dose at night. For children of 1-2 years of age, the dose is 200 mg OD. For heavy infestations, the dose may be repeated for 3 days. It can be considered as an alternative drug for threadworm in a dose of 400 mg OD for 3 days. It is also an alternative drug for pinworms in a dose of 400 mg OD to be repeated after two weeks. Albendazole in addition to Diethylcarbamazine or Ivermectin is a synergistic combination for treating lymphatic filariasis.

It is a drug of choice for cutaneous larva migrans in a dose of 400 mg OD for 5 days. It is also a drug of choice for visceral larva migrans in a dose of 400 mg BD for 28 days. It is a drug of choice for various cestodes like cysticercosis and hydatid disease. For both these conditions, the recommended dose is 400 mg BD for 28 days with fatty meals.

It is a drug of second choice for trematode (liver fluke) in a dose of 400 mg BD for 7 days. It is administered on empty stomach when used against intralumenal worms but with a fatty meal when used against tissue parasites. It is because it has higher bioavailability with fatty meal.

**Adverse Effects:**

It is well tolerated and has rare side effects if used for a short period upto one month. If used for 3 months, as in case of hydatid disease, it may cause epigastric distress, headache, alopecia, fatigue and lassitude, insomnia and transient elevation of aminotranferase enzyme. Its long term use during pregnancy should be avoided.

**Mebendazole:**

It is a prototype benzimidazole.

**Pharmacokinetics:**

Its oral absorption is eratic. Absorption is increased if taken with fatty meals. It is extensively metabolised by decarboxylatation in liver. The metabolites are excreted in urine but a part of the absorbed drug is excreted in bile also. Its half-life is 2-6 hours.

**Clinical Uses:**

It is a drug of choice for the treatment of roundworms, whipworms and hookworms. The recommended dose schedule is 100 mg BD for 3 days. It provides a cure rate of 95-100% for pinworm infestation. For control of pinworms, it is taken as a single dose of 100 mg once, which is repeated after two weeks to eradicate ova.

Due to its broad spectrum anthelmintic activity, mixed infections (roundworm + hookworm; or roundworm + hookworm + whipworm) respond well to Mebendazole. It is an alternative drug for treatment for trichinosis in a dose of 200 mg TDS initially, increasing over three days to 400 mg TDS and then continued for next 10 days. It is useful for intestinal capillariasis in a dose of 200 mg BD for 21 days; for visceral larva migrans in a dose of 100 mg TDS for 5 days; and for beef tapeworm in a dose of 200 mg BD for 4 days. Mebendazole tablets are to be chewed before swallowing. No post-drug purging is necessary with its use.

**Adverse Effects:**

It is relatively safe but can cause abdominal discomfort, nausea, vomiting and diarrhoea. With higher doses, rash, urticaria and elevation of aminotransferase enzymes have been reported. It is contraindicated in patients of liver cirrhosis. It is also contraindicated in pregnancy.

**Thiabendazole:**

It is rarely used except in special conditions.

**Pharmacokinetics:**

It is rapidly absorbed after oral administration. It chelates with iron but not with calcium. Its half-life is 1.2 hours.

**Clinical Uses:**

It has been replaced by Albendazole and Ivermectin. It is used as an alternative drug to treat thread worms. In case of cutaneous larva migrans, it can be applied topically or given orally. The recommended dose is 25 mg/Kg/day, maximum upto 1.5 gm in two divided doses for two days. The tablets should be chewed before swallowing.

**Adverse Effects:**

It causes dizziness, nausea, vomiting and anorexia. Pruritus, rash, headache, drowsiness and neuropsychiatric problems are less common. Rarely, liver failure or Stevens-Johnson syndrome may occur. It has a metabolite aspargine, because of which urine smells like asparagus. It is contraindicated in pregnancy, hepatic and renal disease.

**Triclabendazole:**

It is a narrow spectrum benzimidazole used in veterinary medicine. When given as a single dose of 10 mg/Kg, it is the drug of choice for human fascioliasis. Sheep liver fluke (*Fasciola hepatica*) affects cattle and sheep and rarely infects human beings. Human beings are infected by eating undercooked crabs or cray fish. The infection is refractory to Praziquantel but responds to Triclabendazole.

**Bithionol:**

It is orally well absorbed and is the drug of choice for the treatment of sheep liver fluke and lung fluke. It is given in a dose of 30-50 mg/kg in two divided doses orally on alternate days for 10-15 days. Adverse effects include anorexia, nausea, vomiting, diarrhoea, dizziness, headache and skin rashes. Most of the adverse effects result as a reaction to antigens released from dying helminth. It should be avoided in children below 8 years of age.

**Diethylcarbamazine:**

It is a synthetic piperazine derivative and is available as a citrate salt.

**Pharmacokinetics:**

It is rapidly absorbed from GIT and is widely distributed in tissues except fat. It is excreted in urine unchanged or as N-oxide metabolite. Its plasma half-life is 2-3 hours if urine is acidic but increases to 8-10 hours if urine is alkaline. Dose adjustments are needed in renal impairment and in patients having urinary alkalosis. Complete excretion of the drug from the body takes 48 hours.

**Clinical Uses:**

It is the drug of choice for lymphatic filariasis due to bancroftian filariasis (*W bancrofti*), brugian filariasis (*B malayi*) and loiasis (*Loa loa*). It is active against both microfilarial and adult worms. Its combination with Albendazole provides synergistic response. For treating onchocerciasis, Ivermectin is preferred. The recommended oral dose is 50 mg on first day, 50 mg TDS on second day, 100 mg TDS on third day and then 2 mg/kg TDS for 2-3 weeks. Complete cure may require 2-3 repeated courses. Antihistamine or corticosteroid may be used to limit allergic reaction to dying filariae. It is also used for chemoprophylaxis of loiasis in a dose of 300 mg weekly, and for filariasis in a dose of 50 mg monthly orally. It is also preferred to treat tropical eosinophilia in an oral dose of 2 mg/Kg TDS for 7 days.

**Adverse Effects:**

The adverse effects are of two types: dose-dependent pharmacological effects and allergic reactions to the dying filariae parasite.

Dose - dependent adverse effects are headache, weakness, malaise, anorexia, nausea, vomiting, dizziness and lethargy. Allergic reactions to dying microfilariae are mild in bancroftian, more intense in brugian filariasis, loiasis and specifically in onchocerciasis. These are manifested as fever, lymphadenopathy, cutaneous swelling, leukocytosis, eosinophilia, oedema, rashes, proteinuria. In severe cases, renal haemorrhage and encephalopathy may be observed. In onchocerciasis, the microfilariae dying in the eye can lead to optic neuritis and visual field loss.

**Doxycycline:**

It was reported that an intracellular bacteria, *Wolbachia* lives inside the filarial and onchocerca nematodes. These bacteria are transmitted through parasite eggs and are necessary for the oogenesis in adult female parasites. If these bacteria are eradicated by Doxycycline, then the adult female filarial parasite is incapable to reproduce. Thus 8 week course of 200 mg/day Doxycycline eliminates 95% of microfilariae. A combination of Doxycycline and Ivermectin can provide complete removal of microfilariae.

**Ivermectin:**

It is a semisynthetic microcyclic lactone derived from *Streptomyces avermitilis*.

**Pharmacokinetics:**

It is absorbed from GIT after oral administration. It has a plasma half-life of 12 hours. It is excreted mainly in faeces. It has wide distribution in the body.

**Clinical Uses:**

It has a wide spectrum of activity and is active against filarial nematodes, other nematodes and some parasites.

It is the drug of choice in onchocerciasis. A single oral dose of 150 mg/Kg, for patients above 5 years of age is given every 6 months on empty stomach for treatment of onchocerciasis. Corticosteroids may be used to avoid inflammatory reactions. Annual treatment can prevent blindness from ocular onchocerciasis. In lymphatic filariasis it reduces microfilarial load, but does not kill the adult worms. In loiasis, it reduces microfilaria but can produce neurotoxicity.

It is very useful in treating disseminated strongyloidiasis in an oral dose of 200 mg/Kg daily for two consequetive days. It is also effective in cutaneous larva migrans and pediculosis.

**Adverse Effects:**

These include fever, pruritus, arthralgia, lymphadenopathy, sore throat, cough and headache. It should not be used in pregnancy and in children below 5 years of age. The adverse effects can be minimised by antihistamine and analgesic/corticosteroids.

**Levamisole:**

It is an active Levo-isomer of tetramesole and has a restricted use to treat ascariasis and hookworm infestation. For ascariasis, a single oral dose of 50 mg Levamisole (for children with 10-20 kg body weight), 100 mg (for children with 21-40 Kg body weight) and 150 mg

for adults are recommended. For hookworm or mixed roundworm-hookworm infection in adults, 300 mg is given as a single oral dose over two days. Children are given 6 mg/kg orally once for two days.

It is also an immunostimulant and restores depressed T-cell functions. When given as a single dose for treatment of roundworm or hookworm infestation, adverse effects are limited to nausea, vomiting, abdominal discomfort and headache. Long term use results in influenza-like syndrome, hypersensitivity, arthralgia, muscle pain, abnormal taste in mouth and rarely thrombocytopenia.

**Metrifonate:**

It is an organophosphorous compound useful in bilharziasis caused by *Schistosoma haematobium*. It has good oral absorption. It is not effective against eggs and they continue to pass into urine for several months after killing adult worms. It is given as a single oral dose of 7.5-10 mg/Kg TDS at intervals of 2 weeks.

It is well tolerated and may cause cholinergic adverse effects like diarrhoea, tremors, nausea, vomiting, broncho-spasm and sweating. It is contraindicated in pregnancy, recent insecticide exposure or with drugs like Succinylcholine.

**Niclosamide:**

It is a chlorinated salicylamide and is used for treatment of cestodes (tapeworm). It is not absorbed from GIT; hence high concentrations can be achieved in the lumen. It affects proximal segment of most cestodes resulting in their detachment from the intestinal wall and evacuation by normal peristalitic action. It is not ovicidal. It has been superseded by better drugs like Praziquantel and benzimidazoles. The recommended oral dose is 2 gm OD in the morning over empty stomach. The tablet is to be chewed thoroughly before swelling. It is not effective against cycticercosis and hydatid disease. It may cause abdominal discomfort, nausea and loose stools. Consuming alcohol with Niclosamide can cause antabuse type reaction.

**Oxamniquine:**

It is a tetrahydroquinoline derivative with restricted activity against *Schistosoma mansoni*. It is given orally and is readily absorbed from GIT. The fluke esterifies Oxamniquine to produce a reactive metabolite which alkylates DNA of flukes. It is not active against *S haematobium and S japonicum*. It has been used in combination with Metrifonate for mixed schistosomal infections.

Common adverse effects are drowsiness, dizziness, dullness and headache. Higher doses may cause seizures. Other adverse effects include nausea, colic, pruritus and urticaria. It is contraindicated in pregnancy and epileptic patients.

**Piperazine:**

It is an alternative drug for ascariasis and pinworm. It is not used other helminth infections. It is given orally and is readily absorbed from GIT. For ascariasis, the adult dose is 4 gm once a day for two consequetive days. For pinworm, the adult dose is 2 gm once a day for 7 days. Concomitant use of senna purgative at night helps in expulsion of worms.

Adverse effects include nausea, vomiting, andominal pain and headache. Neurotoxic and allergic reactions are rare. It is contraindicated in pregnancy. It should be avoided in patients of epilepsy and those with impaired renal and hepatic functions. Concomitant use with Pyrantel pamoate should be avoided.

**Praziquantel:**

It is a synthetic isoquinoline-pyrazine derivative.

**Pharmacokinetics:**

It is readily absorbed after oral administration. It undergoes significant first-pass effect in the liver and is converted into inactive hydroxylated metabolites. Its plasma half-life is 1-3 hours. Plasma concentration increases when taken with high carbohydrate meal. Bioavailability is reduced with concomitant use of Phenytoin, Carbamazepine and Dexamethasone.

**Clinical Uses:**

It is a drug of choice for schistosomiasis possessing activity against male and female adults in immature stages. For *S mansoni and S haematobium*, the oral dose is 20 mg/Kg BD, while for *S japonicum and S mekongi*, the oral dose is 20 mg/Kg TDS. In both the cases, the dose intervals should be of 4-6 hours. It is very effective against all flukes except *F hepatica*. The recommended oral dose is 75 mg/Kg once or twice for 2 days.

It is also effective against tapeworm infections. For *T solium and T saginata*, it is administered as a single dose of 10 mg/Kg in the morning. For *D latum and H nana*, a single dose of 15-25 mg/Kg in the morning is suggested. Its efficacy against tapeworm is similar to Niclosamide.

It is considered equivalent to Albendazole in treating neurocysticercosis. 50 mg/Kg daily in three divided doses for 15 days kills the larvae lodged in brain and other tissues. It should not be given with corticosteroids because of reduction in bioavailability.

**Adverse Effects:**

These include drowsiness, dizziness, headache, nausea, vomiting, abdominal pain, pruritus, urticaria, skin rashes with eosinophilia. The safety in children below 5 years of age is not established. It should be avoided in pregnancy. It is contraindicated in ocularcysticercosis due to risk of severe eye damage resulting from occlusion due to dead parasites.

**Pyrantel Pamoate and Oxantel Pamoate:**

Pyrantel pamoate is a tetrahydropyrimidine derivative and Oxantel pamoate is its analogue.

**Pharmacokinetics:**

Only a small fraction of the dose is absorbed from GIT. High levels are achieved in the intestinal tract. It is active against luminal helminths.

**Clinical Uses:**

Pyrantel pamoate is active against several nematodes like roundworms, hookworms and pinworms. The standard dose is 10 mg/Kg, maximum upto 1 gm, given orally as a single

dose. For pinworms, the dose is repeated after two weeks. For heavy infestation with *N americanus*, a consequetive 3 day course is suggested. Pyrantel is not effective against whipworms but Oxantel is effective. A combined formulation of both drugs is available to achieve a broad spectrum nematodal activity.

**Adverse Effects:**

They may cause headache, dizziness and drowsiness. It should be avoided in pregnancy and in children below 2 years of age.

**Preparations:**

- Albendazole: 400 mg tab, 200 mg/5 ml suspension: **Zentel, Zobend, Bandy, Wormin-A.**
- Mebendazole : 100 mg tab, 100 mg/5 ml suspension: **Wormin, Mebex;** 100 mg tab: **Mebazole, Mendazole.**
- Diethylcarbamazine: 50 mg, 100 mg tab, 50 mg/5 ml, 120 mg/5 ml syrup: **Hetrazan, Banocid;** (Diethylcarbamazine 50 mg + Chlorpheniramine 1.25 mg) tab: **Unicarbazan;** (Diethylcarbamazine 250 mg + Chlorpheniramine 5 mg) tab: **Unicarbazan forte.**
- Ivermectin: 6 mg, 12 mg tab: **Vermectin, Scavista;** (Ivermectin 6 mg + Albendazole 400 mg) tab: **Bandyplus.**
- Levamisole: 50 mg, 150 mg tab, 50 mg/5 ml syrup: **Dewormis, Dicaris, Vermisol.**
- Niclosamide: 500 mg tab: **Niclosan.**
- Piperazine: 500 mg tab, 750 mg/5 ml syrup: **Piperazine citrate.**
- Praziquantel : 600 mg tab: **Cest;** 500 mg tab: **Cysticide.**
- Pyrantel: 250 mg tab, 250 mg/5 ml suspension: **Expent, Nemocid.**

## 3.6 ANTIMALARIAL DRUGS

Malaria is a tropical disease caused by sporozoites of plasmodium which are transmitted to humans by the bite of female mosquito of the genus *Anopheles* which has previously sucked blood from a preson infectd with malaria. All attempts to eradicate malaria have failed due to emergence of both drug-resistant strains of malarial parasites and insecticide-resistant strains of *Anopheles*. The symptoms of malaria include chills and rigors followed by fever, headache and sweating. The incubation period for malaria is of 10-30 days.

**Life Cycle of Malarial Parasite**

The malarial prarsite is a single cell protozoan called *Plasmodium*. Clinically important species are *Plasmodium falciparum, P vivax, P ovale and P malariae*. Out of these four types, *P falciparum and P vivax* are the most common species responsible for malaria in India.

The malarial parasite, *Plasmodium* has a complex life cycle consisting of two parts: Sexual cycle and asexual cycle. The sexual cycle takes place in the mosquito and asexual phase occurs in human being. Mosquito is termed as definitive host and human beings as

intermediate host. The life cycle is depicted in Fig. 3.7. Initially, a female is infected by biting a malarial patient whose blood contains male and female gametes of the parasite. The gametes are resistant to the digestive juice of mosquito. Fertilization occurs in the gut of mosquito and the oocysts i.e. encysted zygotes liberate matured sporozoites i.e. spores, which then migrate in the mosquito's salivary glands. During next bite of the mosquito, these sporozoites are passed into the blood of another human being to begin the asexual cycle. The sporozoites can survive hardly for an hour in circulation and seek shelter in liver parenchymal cells where they divide and develop into multinucleated schizonts. This is called as pre-erythrocytic state of the life cycle during which the host is asymptomatic. The primary tissue schizonts from liver mature within 8-21 days to form mononucleated merozoites, which is then liberated by the liver and released into the blood stream. See figure 3.7.

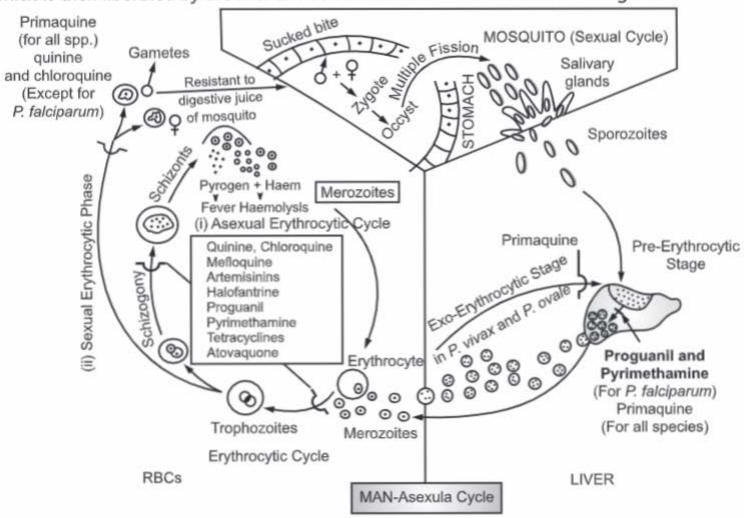



**Fig. 3.7**

In case of *P falciparum*, all merozoites enter erythrocytic schizogony i.e. asexual reproduction of the plasmodium in the RBC of human host. During this stage, the merozoites invade the erythrocytes and form trophozites i.e. motile intracellular parasites-a stage during the growth of protozoa. During their maturation in RBCs, the host's haemoglobin is digested and transported to parasite's food vacuole where it provides amino acids from globin component. The haeme component is made harmless by polymerisation to haemozoin by parasite haem polymerase. Following mitotic replication of its nucleus, the parasites in RBCs are called as blood-schizonts, which after schizogony produce more merozoites. The RBCs

infected with merozoites rupture causing release of several merozoites in the blood stream which are responsible for fever. The liberated merozoites bind to and invade fresh erythrocytes thus continuing asexual erythrocytic cycle. If all the schizonts and merozoites from the asexual phase are not fully eradicated, then the fever may subside temporarily but may reappear when surviving merozoites enter the erythrocytic phase again. This is called as recrudescence of falciparum malaria.

Some merozoites, after entering the erythrocytes differentiate in to male and female forms called as gametocytes. This is called as sexual erythrocytic phase of the life cycle. These gametocytes can complete their life cycle only when the diseased person is bitten by the mosquito at this time. The gametes then reach the mosquito's gut, fertilise to form a zygote which then develops into an oocyst. The rupture of oocysts releases sporozoites, which then migrate to mosquito's salivary gland and enter another host as described above.

In case of *P vivax or P ovale*, a part of schizonts, after release from pre-erythrocytic schizogony phase, re-enter liver parenchymal cells and form dormant hypnozoites, which are sleeping form of parasite. This phase is called as exo-erythrocytic state. This stage may last for several months but can be reactivated later to schizonts which release merozoites which undergo erythrocytic schizogony leading to relapse of malarial fever.

**Classification of Antimalarial Drugs:**

**Based on chemical structure:**

1. 4-Aminoquinolines: eg Chloroquine.
2. Cinchona Alakloids: eg Quinine.
3. Quinoline-methanol: eg Mefloquine.
4. Acridine: eg Mepacrine.
5. 8-Aminoquinolines: eg Primaquine.
6. Biguanides: eg Proguanil.
7. Diaminopyrimidines: eg Pyrimethamine.
8. Artemisin Derivatives: eg Artesunate.
9. Phenanthrene methanol: eg Halofantrine.
10. Napthoquinone: eg Atovaquone.
11. Antibiotics: eg Tetracycline.
12. Sulphonamides and Sulphones: eg Sulfadoxine.

**Based on Affected Plasmodial State**

**Schizonticides:**

These drugs kill the schizonts of the malarial parasite. They are of two types:

**Tissue (hepatic) schizonticides:** These drugs destroy hepatic schizonts soon after infection. See figure 3.7. They are of two types: primary tissue schizonticides and secondary schizonticides. **Primary tissue schizonticides** act on pre-erythrocytic state, eg Proguanil and Pyrimethamine. Both these drugs act against pre-erythrocytic state of *P falciparum* but not of

P vivax and *P ovale*. **Secondary tissue schizonticides** act on exo-erythrocytic state in liver, eg Primaquine. However, Primaquine acts on pre-as well as exo-erythrocytic stage of all plasmodial species.

**Blood schizonticides:** These drugs destroy the blood schizonts viz, merozoites → schizonts → merozoites; and prevent erythrocytic schizogony to terminate the attack of malarial fever. See figure 3.7. They are further subdivided as **fast acting high- efficacy blood schizonticides and slow acting low-efficacy blood schizonticides.** Examples of the first category are Chloroquinine, Quinine, Mefloquine, Lumefantrine, Artemisinine and Atovaquone. They can be used singly to terminate the attack of malaria promptly. The examples in second category are Pyrimethamine + Sulphadoxine/ Proguanil + Doxycycline. They can be used only in combination to terminate the clinical attack.

**Gametocides:**

These drugs destroy the gametocytes or make them ineffective in the host's blood so that mosquitoes cannot transmit the disease, eg Primaquine for all four species of plasmodium; Chloroquinine and Quinine all species except *P falciparum*.

**Sporontocides:**

These drugs make the gametocytes ineffective within the body of the mosquito. Pyrimethamine and Proguanil, which are blood schizonticides, are also sporontocides. However there is no clinical advantage in using these drugs for the purpose.

**Based on Clinical Use:**

**Causal Prophylactics:**

These drugs prevent maturation of sporozoites to schizonts within the infected hepatic cells. Proguanil and Pyrimethamine act as causal prophylactics only against *P falciparum*; while Primaquine acts against all plasmodial species. However Primaquine lacks favourable toxic profile to be used for clinical purpose. If G6PD levels are normal, it can be used in a single dose of 0.5 mg/Kg daily as long as the person remains in endemic malarial region. G6PD is an enzyme, deficiency of which shows abnormal responses to the drug, Primaquine.

**Suppressive Prophylaxis (Chemoprophylaxis):**

Drugs used for this purpose do not affect the hepatic phase of the malarial parasite but destroy the merozoites released from the liver so that development of the erythrocytic stage is prevented. Such drugs are mainly blood schizoticides. Suppressive prophylaxis is employed during the periods of exposure to infected mosquitoes and for some weeks to follow. Following drugs are used for the purpose: Chloroquine, Mefloquine, Proguanil and Doxycycline.

**Suppressive Cure:**

If the suppressive prophylaxis is continued for a longer time, the hepatic phase of hypnozoites becomes extinct or exhausted. It is like a radical cure but by an extended suppressive prophylaxis therapy.

**Clinical Cure:**

The fast-acting high-efficacy blood schizonticides like Chloroquine, Quinine, Mefloquine, Artemisinin, Lumefantrine and Atovaquone can be used singly to treat attacks of *P falciparum* where any delay in the treatment can be fatal. Since *P falciparum* displays no exo-erythrocytic cycle, the clinical cure itself is a radical cure. For Chloroquine resistant falciparum malaria, Quinine is an alternative. The slow-acting low-efficacy blood schizonticides like Proguanil, Pyrimethamine with Sulphadoxine and Tetracycline can be used for clinical cure, but they are used in combination.

For complicated *P falciparum malaria,* eg cerebral malaria, the treatment may be parenteral (IM/IV) drugs like Quinine/Artesunate/Artemether/Arteether. Other drugs may be substituted later as the condition improves.

**Radical Cure:**

Eradication of both exo-erythrocytic and erythrocytic state of malarial parasite leads to radical cure of malaria. An adequate clinical cure of *P falciparum* with Chloroquine results in radical cure. However, in case of *P vivax and P ovale* relapse due to reactivation of hypnozoites in exo-erythrocytic stage is possible at a later stage. In case of *P vivax,* Primaquine administered orally daily for 15 days provides radical cure. Usually Primaquine is given immediately after the use of Chloroquine to achieve a high radical cure rate.

**Individual Drugs:**

**Chloroquine:**

It is a synthetic 4-Aminoquinoline derivative available as Chloroquine phosphate for oral use.

**Pharmacokinetics:**

It is given orally or by intramuscular injection or by slow IV infusion. It is completely absorbed from GIT. It has a large volume of distribution and is extensively bound to liver and other body tissues including cornea and RBCs. It is metabolised by the liver. Initially it has a half-life of 3-4 days; but since it is slowly released from tissues, the terminal half-life may be extended to 1-2 months.

**Mechanism of Action:**

It has a preferential accumulation in parasitized erythrocytes. Since it is basic in nature, it diffuses freely into the parasite lysosome. Inside the lysosome due to acidic pH it gets ionised and being impermeable gets trapped inside the parasite. Its accumulation in parasite's food vacuoles inhibits peptide formation and reduces synthesis of amino acids necessary for parasite viability. It also inhibits the enzyme haem polymerase of the parasite and protects the host's haem from being converted to haemozoin. Free haem is toxic to the malarial parasite.

**Antimalarial Action and Clinical Use:**

It is active during asexual erythrocytic state and is gametocidal only for *P vivax and P ovale* but not for *P falciparum*. Resistance to Chloroquine for the strains of *P falciparum* is

common. It is effective in all types of malaria except for Chloroquine-resistant *P falciparum* malaria. It is used for chemoprophylaxis in visitors temporarily residing in an area where *P falciparum* is not resistant to Chloroquine. It is also used in suppressive cure of *P vivax* malaria, after leaving the endemic area, by giving an extended suppressive prophylactic therapy. In case of *P vivax and Povale* malaria it provides clinical cure but there may be relapse if Chloroquine is not followed by Primaquine.

For chemoprophylaxis, Chloroquine in a dose of 600 mg as free base is used on the first and last day. In between 300 mg weekly dose is given. At the end Primaquine in a dose of 0.5 mg/Kg is added orally. For clinical cure, 600 mg loading dose is followed by 300 mg after 8 hours (first day) and then 300 mg daily for next 2 days orally. It is safe in pregnancy and in younger children above 2 years of age.

In addition to antimalarial use, Chloroquine is used in the treatment of rheumatoid arthritis and for amoebic abscess, not responding to Metronidazole.

**Adverse Effects:**

The observed adverse effects are nausea, vomiting, dizziness, headache, urticaria and rarely blurred vision. Large doses may precipitate retinopathy. Bolus IV injection may cause hypotension and T-wave abnormalities in ECG.

**Contraindications and Drug Interactions:**

- It should be avoided in patients with retinal and visual field abnormalities.
- It aggravates the attacks of psoriasis or porphyria and should be contraindicated in these conditions.
- In patients deficient with G6PD, it may cause haemolytic anaemia.
- $Ca^{++}$ and $Mg^{++}$-containing antacids decrease its absorption.
- Concomitant use of Metoclopramide may precipitate extra-pyrimidal side effects.

**Amodiaquine:**

Its actions are similar to that of Chloroquine. It was withdrawn because of risk of agranulocytosis and hepatotoxicity but has been reintroduced because it is cheap and useful for Chloroquine-resistant *P falciparum* malaria. It may be used in combination with Artesunate/Pyrimethamine-Sulphadoxin. When used in combination, the dose is reduced and fear of adverse effects is less. It is used in area with high prevalence of resistant falciparum malaria as a combination.

**Piperaquine and Pyronaridine:**

**Piperaquine** is a analogue of Chloroquine. It is used for the treatment of *P falciparum* malaria in a fixed dose combination with Dihydroartemisinin. It has a half-life of 35 days, which is beneficial in reducing the rates of relapse.

**Pyronaridine** is an analogue of Amodiaquine. It is used with Artesunate for the treatment of Chloroquine-resistant *P falciparum and P vivax* malaria. It is orally effective and has less relative toxicity.

**Quinine:**

It is an alkaloid derived from Cinchona bar and is the oldest drug used for treatment and prevention of malaria.

**Pharmacokinetics:**

It is given orally but can also be given by slow IV infusion. It is well absorbed when given orally. It is widely distributed in body tissues. It is metabolised in liver and excreted in urine. Its half-life is 10-12 hours.

**Mechanism of Action:**

It inhibits the parasite's haem polymerase but it is not so extensively concentrated in the malarial parasite as that of Chloroquine. It acts as a protoplasmic poison to the parasite and poisons the parasite's feeding mechanism by hampering supply of aminoacids and peptides.

**Antimalarial Action and Clinical Use:**

It acts on asexual erythrocytic state and has gametocidal activity only against *P vivax and P ovale* but not on pre- and exo-erythrocytic state of *P falciparum*. It is the main Antimalarial drug for treating Chloroquine-reisitant *P falciparum* malaria.

The treatment is given with a loading dose to achieve effective plasma concentration. It can be administered as a slow intravenous injection in divided doses or a slow continuous IV infusion. As soon as the condition of the patient improves, the drug can be administered by oral therapy.

For clinical cure while treating *P falciparum*-resistant malaria, it is given in a dose of 600 mg orally TDS for 7 days alone or in combination with Pyrimethamine 75 mg + Sulphadoxine 1500 mg as a single oral dose; or with Tetracycline 250 mg QID for 7 days or with Doxycycline 100 mg OD orally for 7 days.

Besides antimalarial use, it is also used to treat nocturnal leg cramps observed in patients of varicose veins, diabetes and arthritis. Quinine + Clindamycin is a first line therapy for the treatment of babesiosis, a tick-borne malaria like disease.

**Adverse Effects:**

It is bitter in taste; hence oral compliance is poor. Being irritant to gastric mucosa, it can cause nausea and vomiting. Bolus IV administration can cause hypotension and cardiac arrhythmia. Higher plasma levels can lead to cinchonism-a toxic state characterised by sweating, tinnitus, blurred vision, headache, diarrhoea and cardiac arrhythmia. In high doses, it is potentially neurotoxic. Haematologic toxicity includes haemolysis, especially in G6PD deficient patients. It stimulates insulin release and may cause hypoglycaemia. Hence it is usually infused with 5% glucose solution. In severe *P falciparum* malaria, glucose consumption by the parasite is increased, which also causes hypoglycaemia. All this may cause hypoglycaemic coma. Another rare consequence of eratic use of Quinine can cause "black water fever". It is a hypersensitivity manifested by haemolysis with renal failure.

**Contraindications and Drug Interactions:**

- It is contraindicated in persons having visual and auditory problems.
- It is also contraindicated in patients with cardiac abnormality.
- $Al^{+++}$ and $Mg^{++}$-containing antacids decrease its absorption.
- Quinine raises plasma level of Digoxin and
- Quinine should not be given with Mefloquine because of possible adverse effect on cardiac conduction.

**Mefloquine:**

It is chemically related to Quinine.

**Pharmacokinetics:**

It is well absorbed orally. It is not given parenterally due to pain and local irritation at the site of injection. It is highly protein bound and extensively distributed in body tissues. It undergoes entero-hepatic circulation and is eliminated slowly. It has half-life of 20 days allowing weekly dosing for chemoprophylaxis and single dose regimen for clinical cure.

**Mechanism of Action:**

It resembles Quinine. It is potent blood schizonticide against *P falciparum, Pvivax and P ovale*. It is neither tissue schizonticidal nor gametocidal. It is used for chemoprophylaxis or for clinical cure but not for severe or complicated malaria.

For chemoprophylaxis, the dose is 200 mg weekly orally or 500 mg fortnightly; starting a week before and ending 4 weeks after leaving. For clinical cure, the dose is 750 mg orally followed by 500 mg 12 hours later.

**Adverse Effects:**

It causes nausea and vomiting, when used for chemoprophylaxis. When used for an acute attack, neuropsychiatric adverse effects may be observed which include vertigo, confusion and rarely vivid dreams or seizures. There are few reports of abnormal AV conduction. It should be avoided during pregnancy. It should not be coadministered with Quinine or Halofantrine, which may aggravate conduction defects. If neuropsychiatriac adverse effects are observed, the drug should be discontinued.

**Quinacrine and Mepacrine:**

Both drugs are erythrocytic schizonticides and are less effective and more toxic than Chloroquine. Hence they are not preferred. They may cause vertigo, abdominal cramps, nausea, vomiting and rarely psychosis. Long term use may cause discolouration of skin and eyes.

**Prinaquine:**

It is a synthetic 8-aminoquinoline derivative.

**Pharmacokinetics:**

It is well absorbed orally. It is widely distributed. It is not bound extensively to the tissues. It is rapidly metabolised by liver and excreted in urine. Its half-life is 3-6 hours. Its metabolites are active but have a higher potential for toxicity.

**Mechanism of Action:**

Its quinone metabolites inhibit the coenzyme-Q govern respiratory process of the parasite in the exo-erythrocytic state. The metabolites are responsible for haemolytic adverse reaction.

**Antimalarial Action and Clinical Use:**

It is active against pre-erythrocytic state, exo-erythrocytic state-hypnozoites. It is gametocidal but has no action on asexual erythrocytic state. Resistance to *P vivax* is rare. It is greater used in preventing relapse for *P vivax and P ovale* malaria. It is the only effective drug against the exo-erythrocytic and pre-erythrocytic forms of all malarial parasites. It is suggested that G6PD status of the patient should be evaluated prior to prescribing this drug.

**Non-antimalarial Use:**

A combination of Clindamycin and Primaquine offers improved tolerance over high dose Cotrimoxazole in treating moderate *Pneumocystis giroveci* pneumonia.

**Adverse Effects:**

Higher doses or prolonged use causes GIT distress, nausea, headache, pruritus and leukopenia. In individuals with G6PD deficiency (black race and Mediterranean people), it can cause fatal haemolytic anaemia. It is contraindicated in pregnancy because the foetus is deficient of G6PD; hence there is a risk of haemolytic anaemia.

Other analogues of Primaquine are Bulaquine, Etaquine and Tafenoquine. Bulaquine is a prodrug of Primaquine. It is given in a dose of 25 mg/day for 5 days starting on second day of Chloroquine therapy. Neither Primaquine nor Bulaquine can be given parenterally due to fear of marked hypotension. Etaquine and Tafenoquine are more potent and longer acting analogues of Primaquine. Tafenoquine can be given orally, once weekly.

**Pyrimethamine-Sulfonamide/Dapsone Combinations:**

Pyrimethamine is structurally related to Trimethoprim. Malarial parasites cannot utilise preformed folic acid and they have to synthesise their own folic acid. Pyrimethamine selectively inhibits the plasmodial folate reductase enzyme which converts dihydrofolic acid (DHF) to tetrahydrofolic acid (THF). Non-availability of THF prevents the synthesis of pyrimidines and purines which are essential for plasmodial nucleic acid synthesis.

**Pharmacokinetics:**

Pyrimethamine is well absorbed after oral administration. Its elimination half-life is 3-4 days. It can be administered once a week.

**Antimalarial Action and Clinical Use:**

Pyrimethamine is a slow acting erythrocytic schizonticide for all malarial species. It exhibits weak activity against pre-erythrocytic state of *P falciparum*. It has no gametocidal activity. If used alone, resistance develops rapidly. It is highly effective when used in combination with Sulphonamides like Sulfadoxin or Sulphamethopyrazine or with Dapsone. The combination causes a sequential blockade of folic acid synthesis at different stages. Hence the combination has synergistic action and least resistance.

Sulfadoxin + Pyrimethamine or Dapsone + Pyrimethamine are not recommended for chemoprophylaxis of malaria due to resistance and toxicity. The toxicity is expressed as exfoliative dermatitis, Stevens-Johnson syndrome. The combinations are used for clinical cure of *P falciparum malaria*. The Sulfadoxin + Pyrimethamine combination can be used as an adjunct with Quinine to treat Chloroquine-resistant *P falciparum malaria*.

**Other Uses:**

Pyrimethamine (50-75 mg/day) with Sulfadoxine (2-4 gm/day) for 1-3 weeks is the first line therapy for toxoplasmosis in immunodeficient patients. Folinic acid is added to the therapy to counteract megaloblastic anaemia. The doses are then reduced to 50% and continued for another 4-5 weeks. Alternatives include Pyrimethamine + Clindamycin/Clarithromycin or Azithromycin.

**Adverse Effects:**

In high doses, Pyrimethamine may inhibit mammalian dihydrofolate reductase enzyme and may induce megaloblastic anaemia. If used during pregnancy, folic acid supplements must be added. Other toxic symptoms include anorexia, vomiting, atrophic glossitis and CNS stimulation including seizures. The Pyrimethamine + Sulfadoxine combination can cause various skin reactions like Stevens-Johnson syndrome, allergic alveolitis and blood dyscrasias. Large doses of Pyrimethamine + Dapsone can cause haemolytic anaemia, agranulocytosis and eosinophilic alveolitis.

**Proguanil (Chloroguanide):**

**Pharmacokinetics:**

It is rapidly absorbed after oral administration. Its elimination half-life is 16 hours. It is administered once daily.

**Mechanism of Action:**

It is a inhibitor of plasmodial dihydrofolate reductase. It has a slow action against the erythrocytic forms of all four human malarial species. It has an additional schizonticidal effect on pre-erythrocytic state but not on hypnozoites of *P vivax*.

**Antimalarial Action and Clinical Use:**

Proguanil alone is not recommended for chemoprophylaxis because of possibility of resistance. The combination of Chloroquine (300 mg/week) and Proguanil (200 mg/day) is preferred as an alternative to Mefloquine because the combination is relatively less toxic. A combination of 250 mg of Atovaquone + 100 mg of Proguanil once daily for 2 days prior to and 7 days after the exposure is a preferred regimen for chemoprophylaxis for *P falciparum* malaria. Alternatively, 1 gm of Atovaquone + 400 mg Proguanil once daily for 3 days is a preferred regimen for the treatment of Chloroquine-resistant *P vivax* and multidrug-resistant *P falciparum* malaria. Atovaquone + Proguanil is the only recommended combination for the self-treatment of malaria. The combination should be taken with food.

**Adverse Effects:**

If folic acid is taken concurrently, Proguanil is safe for use during pregnancy. It is remarkably safe when used in combination with Chloroquine/Atovaquone/Doxycycline.

**Atovaquone:**

Proguanil potentiates Antimalarial action of Atovaquone. Hence fixed dose oral combination of Atovaquone + Proguanil prevents resistance and is better tolerated as well as safer than either drugs used alone.

**Pharmacokinetics:**

It is administered orally. Its bioavailability is poor and eratic but it is increased by fatty meal. It is highly protein bound (99%). It has a long plasma half-life of 2-3 days, partly due to enterohepatic recycling. It is excreted unchanged exclusively in faeces.

**Mechanism of Action:**

It disrupts the plasmodial mitochondrial electron transport of respiratory process. This results in the collapse of plasmodial mitochondrial functions and inhibition of pyrimidine and ATP synthesis.

**Therapeutic Uses:**

It is useful for following indications:

- Chemoprophylaxis and treatment of *P falciparum* malaria where it is used with Proguanil. The combination has potent activity against asexual erythrocytic stage of *P falciparum*. It is also active against per-erythrocytic state but not against *P vivax* hypnozoites.
- Acute oral treatment of mild to moderate *Pneumocystitis carinii* pneumonia in patients who are intolerant to Cotrimoxazole in a dose of 750 mg TDS orally for 21 days.
- Treatment or suppression of *Toxoplasma gondii* encephalitis.

**Adverse Effects and Drug Interaction:**

They include abdominal pain, nausea, vomiting, headache, reversible elimination in liver enzyme and rarely rash. Concurrent use of Metoclopramide, Tetracycline or Rifampicin reduces Atovaquone plasma levels by 40-50%; hence Promethazine should be preferred as an antiemetic.

**Artemisinin Derivatives:**

Artemisinin, Artesunate, Artemether and Arteether are sesquiterpene lactone derivatives obtained from a Chinese herb *Artemisia annua*. Artemisinin is a prodrug and is rapidly metabolised to an active metabolite Dihydroartemisinin. Artesunate, Artemether and A teether are semisynthetic derivatives of Artemisinin with improved potency and better bioavailability. Artesunate is a water soluble derivative of dihydroartemisinin. It can be given orally, IV, IM or rectally. Atemether is a oil soluble methyl ether of Dihydroartemisinin. It can be used orally or IM. Arteether is a oil soluble ether of Dihydroartemisinin. It is administered only by intramuscular route.

**Pharmacokinetics:**

The plasma half-life of Artesunate is less than 1 hour. The plasma half-life of Artemether is 4-11 hours depending on route of administration; while Arteether has an elimination life of 23 hours.

Compared to other antimalarials, Artemisin derivatives act rapidly and are many fold active against the asexual erythrocytic state of *P vivax, P ovale and P falciparum* malaria.

**Mechanism of Action:**

Initially, the intraparasitic ferrous protoporphyrin-IV present in parasitic food vacuole catalyses breakdown of endoperoxide bridge of Artemisinin molecule. This is followed by generation of highly reactive free radicals which damage the parasite membrane by covalently binding to membrane proteins.

They have little gametocidal action but do not have any effect on pre-erythrocytic or exo-erythrocytic hypnozoites state of liver.

**Therapeutic Uses:**

They are restricted to the clinical cure of severe falciparum malaria including cerebral malaria and in Chloroquine or multidrug-resistant malaria. Their use for Chloroquine-sensitive *P falciparum* malaria or for other uncomplicated malaria is not justified. Their use for chemoprophylaxis of malaria is irrational.

The treatment of malaria employs Artemisinin based Combination Therapies (ACTs). Five such regimens are recommended. They are as follows:

- Artemether + Lumefantrine
- Artesunate + Mefloquine
- Artesunate + Amodiaquine
- Artesunate + Pyrimethamine-Sulfadoxine
- Dihydroartemisinin + Pipreaquine

**Adverse Effects:**

They are better tolerated. Yet nausea, vomiting, abdominal pain, itching and temporary QT-prolongation may occur.

**Halofantrine and Lumefantrine:**

**Halofantrine** has potent blood schizonticidal properties against all four human malaria species. It is not active against any hepatic stage of malarial parasite. It has no gametocidal activity. Its oral bioavailability is eratic but enhanced with food. Its mechanism of action involves inhibition of plasmodial proton pump.

Its use is highly restricted to treat multidrug-resistant falciparum malaria in a dose of 500 mg QID for 1 day to be repeated after one week. Due to cardiotoxicity and eratic bioavailability, it is not used for chemoprophylaxis.

The most common adverse effects are abdominal pain vomiting, cough, rash, pruritus, transient rise in liver enzyme levels. It causes prolongation of QT or PR interval and dose

related defects in cardiac conduction. Concurrent use of Mefloquine worsens its cardiotoxicity. It is contraindicated in cardiac patients with conduction defects. It should be avoided in pregnancy.

**Lumefantrine** has structural similarity to Mefloquine and Halofantrine. It is used in combination with Artemether for a synergistic Antimalarial effect against multidrug-resistant *P falciparum* malaria. The combination does not cause cardiotoxicity and can be given with fatty meal to increase bioavailability. The combination is to be taken twice daily for 3 days.

**Antibiotics:**

Tetracycline and Doxycycline are blood schizonticidal for all human malarial parasites; but have no activity against any of the liver stages. Doxycycline in a dose of 100 mg/day orally or Tetracycline in a dose of 250 mg QID or 500 mg BD can be used as a second line therapy for chemoprophylaxis of malaria in Chloroquine-resistant *P falciparum* –infested area. Doxycycline in a dose of 200 mg/day can be combined with Quinine or Artesunate to treat multidrug-resistant falciparum malaria.

Clindamycin in a dose of 20 mg/Kg/day orally, TDS for 7 days along with Quinine in a dose of 650 mg TDS orally for 3-7 days is a suggested regimen for Chloroquine-resistant falciparum malaria.

**Preparations:**

- Chloroquine: 250 mg tab, 500 mg DS tab, 100 mg/10 ml suspension, 40 mg/ml injection: **Lariago, Cloquin, Resochon;** 50 mg DS tab, 64.5 ml injection: **Rimaquin.**
- Quinine sulphate: 100 mg, 300 mg, 600 mg tab, 100 mg/5ml suspension, 300 mg/ml injection: **Rez-Q;** 100 mg, 300 mg tab, 300 mg/ml injection: **Quininga.**
- Mefloquine: 250 mg tab: **MQF, Mefque, Meflotas, Mefloc.**
- Mepaquine: 100 mg, 300 mg tab: **Maldin.**
- Primaquine: 2.5 mg, 7.5 mg, 15 mg tab: **Malirid, Malquine, PMQ.**
- Bulaquine: (Bulaquine 25 mg + Chloroquine 500 mg) pack of 5 tabs: **Aablaquin.**
- Pyrimethamine + Sulfadoxine: (Pyrimethamine 25 mg + Sulfadoxine 500 mg) tab, (Pyrimethamine 12.5 mg + Sulfadoxine 250 mg) / 5 ml suspension: **Laridox, Malocide, Reziz, Croydoxin-FM;** (Pyrimethamine 37.5 mg + Sulfadoxine 750 mg) tab: **Piralfin forte.**
- Pyrimethamine + Dapsone: (Pyrimethamine 25 mg + Dapsone 100 mg) tab: **Maloprim.**
- Proguanil: 100 mg tab: **Laveran.**
- Arteether: 150 mg/2 ml injection: **Malther, Z-mal, E-mal.**
- Artemether: 40 mg cap, 80 mg/ml injection: **Larither, Malither;** 80 mg/ml injection: **Paluther;** (Artemether 20 mg + Lumefatrine 120 mg) tab: **Combither, Lumither;** (Artemether 80 mg + Lumefantrine 480 mg) tab : **Combither forte.**
- Artesunate: 50 mg tab, 60 mg/vial injection: **Falcigo, Falcinil, Ulteria;** (Artesunate 50 mg + Mefloquine 250 mg) tab/kit: **Falcigo plus.**

## 3.7 ANTIAMOEBIC AGENTS

Amoebiasis is an intestinal infection of *Entamoeba histolytica*. The infection can be asymptomatic or may present as mild to moderate colitis or as dysentery or liver abscess. Drug therapy is needed not only for acute infection but also for the asymptomatic carrier because the dormant *E histolytica* may prove to be a potential source of infection to others.

**Life Cycle of Amoeba (Entamoeba histolytica)**

Life cycle of *E histolytica* is depicted in Fig. 3.8. *E histolytica* exists in two forms: cysts and trophozoites. Cysts can survive outside the body for several weeks. Trophozoites are labile, live inside the body and are invasive in nature. Cysts are ingested through food or water which is contaminated with infective cysts. Inside the lumen, they are converted to trophozoites which survive on intestinal bacterial flora. These luminal trophozoites can be carried towards the rectum, get converted to cysts in between the pathway and expelled in faeces to cause infection in other persons. Some trophozoites may multiply and invade the mucus of large intestine. This leads to dysentery i.e. blood and mucus in the stool. Alternatively, it may cause intestinal amoebiasis causing vagur coliky pain and amoeboma. At later stage, the trophozoites may pass into the blood stream and may spread to the liver through the portal vein to produce amoebic liver abscess. Rarely amoebic abscess may be found in lungs or the brain. Tissue phase is only secondary to intestinal amoebiasis. Hence, in tissues, only trophozoites are present and not the cysts.

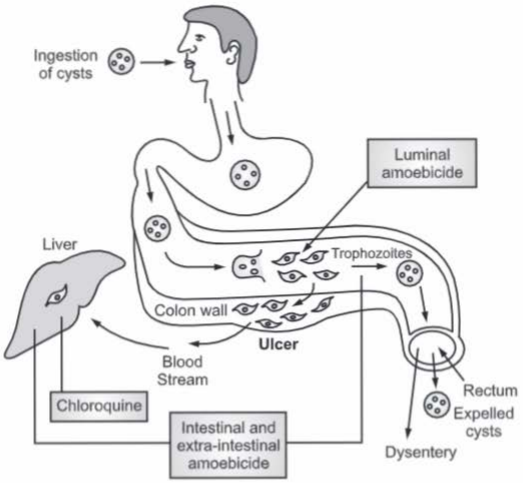



**Fig. 3.8: Life cycle of *Entamoeba histolytica***

**Classification of Antiamoebic Drugs:**

Antiamoebic drugs (Amoebicides) are classified into two types: Tissue amoebicides and luminal (intestinal) amoebicides

**Tissue Amoebicides:**

They are further classified into two sub-types: Intestinal and extra-intestinal; only extra-intestinal. Their examples are indicated below.

**Intestinal and Extra-intestinal Amoebicides:**

The examples in this category are: Metronidazole, Tinidazole, Ornidazole, Secnidazole, Satranidazole and Nimorazole. Chemically, all of them are nitro-imidazoles.

In addition, Emetine and Dehydroemetine are the alkaloids in this category.

**Extra-intestinal amoebicides:** The only drug in this category is Chloroquine.

**Luminal (intestinal amoebicides):** There are three types of luminal amoebicides. The examples in this category are as follows:

- Amides: eg Diloxanide furoate.
- 8-hydroxyquinolines: eg Diidohydroxyquin (Iodoquinol).
- Antibiotics: eg Tetracyclines, Paromomycin.

Nitroimidazole derivative is the major category acting as intestinal and extra-intestinal amoebicides. The prototype drug is Metronidazole. It is discussed in detail below. Comments about other nitroimidazoles are also included.

**METRONIDAZOLE**

It is selectively toxic not only to amoebae, but to certain other protozoa, anaerobic bacteria and certain helminths.

**Pharmacokinetics:**

It is readily absorbed after oral administration. It distributes well throughout the body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, CSF, saliva and breast milk. Its plasma half-life is about 8 hours, which is increased in patients with impaired renal function. The parent drug and its metabolites are excreted in urine.

**Mechanism of Action:**

Anaerobic protozoan parasites, including amoebae possess an enzyme called pyruvate-ferrodoxin oxido-reductase, which is involved in energy production and other metabolic functions through electron transfer reactions. This enzyme is not found in mammalian cells. The nitro group in Metronidazole serves as an electron acceptor. Reduced Metronidazole is cytotoxic to anaerobic bacteria/protozoa and disrupts replication, transcription and repair process of DNA which results in cell death. Aerobic microenvironment prevents reduction of Metronidazole and reduces its cytotoxicity.

**Antimicrobial Spectrum and Clinical Uses:**

It is highly active against *E histolytica, Giardia lamblia, Trichomonas vaginalis* (in both males and females), *Blastocystis hominis, Balantidium coli* and a helminth *Dracunculus medinensis* (guinea worm). It also finds extensive use in infections caused by anaerobic cocci such as *Peptococcus* and anaerobic Gram –negative bacilli like *Bacteroides. A*naerobic Gram-positive bacilli like *Clostridia,* which cause pseudomembranous colitis (PMC) also respond to Metronidazole. In addition, following features are observed with Metronidazole:

- It is a drug of choice for the treatment of extra-luminal amoebiasis. It kills trophozoites but not the cysts and effectively eradicates both intestinal and extra-intestinal amoeba. The recommended dose for intestinal amoebiasis is 400 mg orally TDS for 7 days; for amoebic dysentery and liver abscess, the dose is 800 mg TDS for 7 days.
- It is an effective drug for treating anaerobic bacterial infections such as brain abscess, endocarditis and infections occurring after colo-rectal surgery or appendectomy, when it is used with Gentamycin.

**Adverse Effects and Drug Interactions:**

Most frequently observed adverse effects are nausea, vomiting, metallic taste and epigastric distress. Urine becomes dark red-brown. Less frequently neurotoxic effects like vertigo, dizziness and numbness of extremities have been observed. It inhibits the enzyme aldehyde dehrogenase; hence if taken with alcohol, a Disulfiram-type reaction occurs leading to vomiting. It potentiates anticoagulant effect of Warfarin and lithium toxicity by decreasing its renal elimination. It should be avoided during pregnancy and in persons suffering from neurological complications.

**Tinidazole:**

It is an equally effective analogue of Metronidazole. It is eliminated slowly with a plasma half-life of 12-14 hours. Hence it is more suitable for once/twice daily administration. It is better tolerated and produces lesser incidence of nausea, epigastric distress and metallic taste. Recommended dose for amoebiasis is 600 mg BD for 5-7 days.

**Ornidazole**

It is slowly metabolised with a plasma half-life of 12-14 hours. Its clinical use, dosage regimen and toxicity profile are identical to Tinidazole.

**Satranidazole**

It is similar to Tinidazole but is slightly more potent. It does not cause neurological toxicity and Disulfiram-type reaction with alcohol. Recommended dose for amoebiasis is 300 mg BD for 5 days.

**Secnidazole**

It is similar to Metronidazole. It has a longer plasma half-life of > 20 hours and has a post-anti-protozoal effect. Recommended dose for amoebiasis is 2 gm as a single dose orally. For hepatic amoebiasis, the dose is 1.5 gm once daily orally for 5 days.

**Nimorazole**

It is similar to Metronidazole except for dose schedule. For amoebiasis, the dose is 1 gm BD orally for 5-7 days. It should be taken with food and repeated after one month.

**EMETINE AND DEHYDROEMETINE**

Emetine is an alkaloid from *Cephaelis ipecacuanha*. Dehydroemetine is its synthetic derivative. Both are effective against tissue trophozoites of *E histolytica* and have no effect on cysts. Both act by inhibiting protein synthesis in amoeba. Both are administered orally (SC or IM injection but never intravenously) since oral absorption is eratic. Both accumulate in liver and are eliminated slowly via kidneys. Hence they should be given only till the patient becomes asymptomatic.

They are largely replaced by Metronidazole. They can be used in severe amoebic dysentery, amoebic liver abscess or in situations where Metronidazole cannot be used.

They can cause cardiotoxicity which includes hypotension, tachycardia, cardiac arrhythmia and myocarditis. Dehydroemetine is less cardiotoxic. Nausea and vomiting are frequent. Other adverse effects include diarrhoea, and abdominal cramps and muscle weakness. These drugs should not be used in patients with cardiac or renal disease, in children or in pregnancy. Usual recommended dose is 60 mg IM once daily for 3-5 days; maximum upto 10 days.

**Extra-intestinal Amoebicides:**

The only example in this category is Chloroquine. It is highly concentrated in liver and destroys trophozoites of *E histolytica*. It is very effective in treating hepatic abscess, amoeboma and extra-intestinal amoebiasis. The recommended doses are 500 mg twice daily orally initially for 2 days and then 500 mg once daily for 21 days. Amoeba does not develop resistance to Chloroquine. It is not effective against cysts. Hence a luminal amoebicide should always be given with Chloroquine. Details of Chloroquine are discussed under antimalarial drugs.

**Luminal Amoebicides:**

There are two categories of drugs and a single drug as luminal amoebicides. The categories are 8-hydroxyquinolines and selected antibiotics. The single drug is Diloxanide furoate.

**8-hydroxyquinolines:**

Iodoquinol (diiodohydroxyquin) is a halogenated 8-hydroxyquinoline. It is commonly used with Metronidazole to treat luminal amoebiasis. It kills the cysts forming trophozoites but not the trophozoites present in intestinal wall or extra-intestinal tissues.

Systemic Iodoquinol has a plasma half-life of 12 hours. It is also used to treat superficial fungal skin infection. Recommended doses are 600 mg TDS orally.

It may cause adverse effects like nausea, vomiting, pruritus and green coloured stools. Prolonged use may cause goiter and iodism causing chills, fever, angioedema and inflammation of mucus membranes. Repeated and indiscriminate use can cause Subacute Myelo-Optic Neuropathy (SMON) leading to visual impairment and blindness, particularly in children. It is not recommended in pregnancy and for children.

**Antibiotics:**

These are used as alternatives in the management of mild to moderate intestinal amoebiasis along with Diloxanide furoate or Metronidazole. They reduce the normal gastro-intestinal bacterial flora on which the amoebae thrive for growth. Tetracycline and Doxycycline do not have a direct effect on the protozoa while Paromomycin has a direct amoebicidal action besides reducing GIT bacterial flora. They have no effect against extra-intestinal amoebic infections.

**Diloxanide Furoate:**

It is an effective luminal amoebicide but is not active against tissue trophozoites. It is very effective in mild intestinal amoebiasis and in asymptomatic cyst passers, because it kills trophozoites which produce cysts. It is an ester and is hydrolysed in the gut to Diloxanide and Furoic acid. About 80-90% of free Diloxanide gets absorbed systemically but has no systemic antiamoebic action. About 10-20% unabsorbed drug leads to luminal antiamoebic action. It is not useful in amoebic dysentery. Recommended dose schedule is 500 mg orally TDS for 10 days. Its combined use with Metronidazole or Tinidazole is quite popular. It is well tolerated. The only common complaint is flatulence.

**Preparations:**

- Metronidazole: 200 mg, 400 mg tab, 200 mg/5ml suspension, 500 mg/100 ml IV infusion: **Flagyl, Metrogyl, Aristogyl;** (Metronidazole 400 mg + Diloxanide furoate 500 mg) tab: **Dyrade-MDS, Metrogyl compound;** (Metronidazole 500 mg + Norfloxacin 400 mg) tab: **Normetrogyl, Gramogyl.**
- Tinidazole: 500 mg, 1 gm tab: **Tinifas, Fasigyn;** 300 mg, 500 mg, 1 gm tab, 800 mg/400 ml IV infusion: **Tiniba;** (Tinidazole 600 mg + Diloxanide furoate 750 mg + Dicyclomine 5 mg) tab: **Zoa-forte;** (Tinidazole 600 mg + Norfloxacin 400 mg) tab: **Norflox-TZ, Norbactin;** (Tinidazole 600 mg + Ciprofloxacin 500 mg) tab: **Ciplox-TZ, Zoxan-TZ.**
- Ornidazole: 500 mg tab, 500 mg/100 ml IV infusion: **Dazolic;** 500 mg tab: **Ornida, Ornifen;** (Ornidazole 500 mg + Ofloxacin 200 mg) tab: **Gazal-O.**
- Satranidazole: 300 mg tab: **Satrogyl;** (Satranidazole 300 mg + Ofloxacin 200 mg) tab: **Satrogyl-O.**
- Secnidazole: 1 gm tab: **Seczol, Secnil-forte, Entosec.**
- Nimorazole: 250 mg tab: **Flosogyn.**
- Dihydroemetine hydrochloride: 30 mg/ml injection: **Tilemetin.**

## SUMMARY

**Antitubercular drugs**

- **First line essential drugs**
  - Isoniazide (INH)
  - Rifampicin (RMP)
  - Ethambutol (ETB)
  - Pyrazinamide (PZA)
- **First line supplemental drugs**
  - Streptomycin
  - Rifabutin
  - Rifapentine
- **Second line drugs**
  - Amikacin
  - Capreomycin
  - Ethionamide
  - Para-amino salicylic acid (PAS)
  - Cycloserine
  - Thiacetazine
  - Fluoroquinolines
    - Ciprofloxacin
    - Ofloxacin
    - Levofloxacin
    - Moxifloxacin

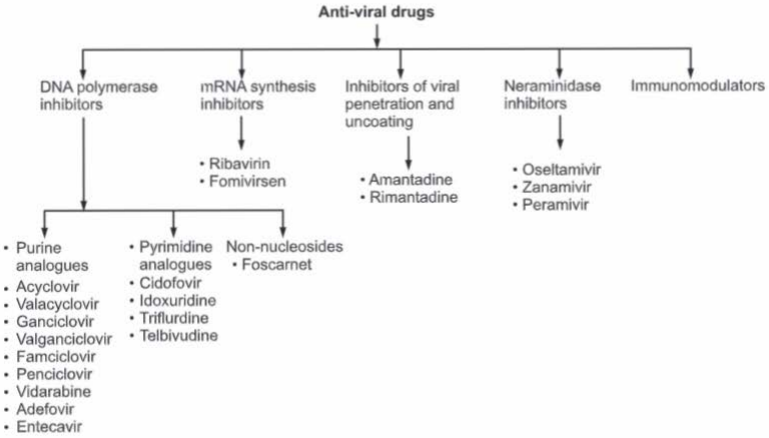
**Antileprotic drugs**

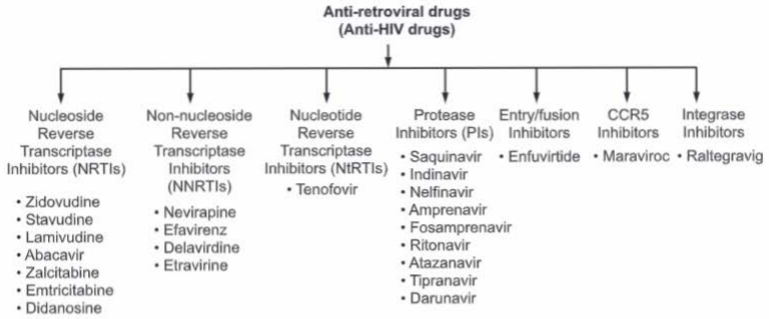
- Dapsone
- Clofazimine
- Rifampicin
- Antibiotics
  - Fluoroquinolones : Ofloxacin, Sparfloxacin, Pefloxacin
  - Macrolides : Clarithromycin
  - Tetracyclines : Minocycline

**Antifungal drugs**

- **For systemic infections**
  - **Echinocandins**
    - Caspofungin
    - Micafungin
    - Anidulafungin
  - **Polyene**
    - Amphotericin B
  - **Azoles**
    - Ketoconazole
    - Fluconazole
    - Itraconazole
    - Voriconazole
    - Posaconazole
  - **Others**
    - Flucytosine
- **For superficial infections**
  - Griseofulvin
  - Nystatin
  - Ciclopirox
  - Tolnaftate
  - Clioquinol
  - Benzoic acid
  - Sodium thiosulphate
  - Azoles : @
  - Alkylamines : Terbinafine, Butenafine, Naftifine

@ : Clotrimazole, Miconazole, Ketoconazole, Butaconazole, Econazole, Oxyconazole, Sulconazole, Terconazole, Tioconazole, Sertaconazole


Anti-viral drugs
DNA polymerase inhibitors
mRNA synthesis inhibitors
Inhibitors of viral penetration and uncoating
Neraminidase inhibitors
Immunomodulators
• Ribavirin
• Fomivirsen
• Amantadine
• Rimantadine
• Oseltamivir
• Zanamivir
• Peramivir
• Purine analogues
• Acyclovir
• Valacyclovir
• Ganciclovir
• Valganciclovir
• Famciclovir
• Penciclovir
• Vidarabine
• Adefovir
• Entecavir
• Pyrimidine analogues
• Cidofovir
• Idoxuridine
• Triflurdine
• Telbivudine
Non-nucleosides
• Foscarnet


Anti-retroviral drugs
(Anti-HIV drugs)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)
• Zidovudine
• Stavudine
• Lamivudine
• Abacavir
• Zalcitabine
• Emtricitabine
• Didanosine
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
• Nevirapine
• Efavirenz
• Delavirdine
• Etravirine
Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)
• Tenofovir
Protease Inhibitors (PIs)
• Saquinavir
• Indinavir
• Nelfinavir
• Amprenavir
• Fosamprenavir
• Ritonavir
• Atazanavir
• Tipranavir
• Darunavir
Entry/fusion Inhibitors
• Enfuvirtide
CCR5 Inhibitors
• Maraviroc
Integrase Inhibitors
• Raltegravig

**Anthelmintics**

- **Benzimidazoles**
  - Albendazole
  - Mebendazole
  - Thiabendazole
  - Triclabendazole
- **Others**
  - Bithionol
  - Diethylcarbamazine
  - Doxycycline
  - Ivermectin
  - Levamisole
  - Metrifonate
  - Niclosamide
  - Oxamniquine
  - Piperazine
  - Praziquantel
  - Pyrantel pamoate
  - Oxantel pamoate

**Anti-malarial drugs**

| | Classes | | Examples |
|---|---|---|---|
| 1. | 4-Aminoquinolines | : | Chloroquine, Amodiaquine, Piperaquine, Pyronavidine |
| 2. | Cinchona alkaloids | : | Quinine |
| 3. | Quinoline methanol | : | Mefloquine |
| 4. | Acridine | : | Mepacrine, Quinacrine |
| 5. | 8-Aminoquinolines | : | Primaquine |
| 6. | Biguanides | : | Proguanil |
| 7. | Diaminopyridines | : | Pyrimethamine* |
| 8. | Artemisinin derivatives | : | Artesunate$, Artemisin, Artemether(a), Dihydroartemisin(b) |
| 9. | Phenanthrene methanol | : | Halofantrine, Lumefantrine |
| 10. | Napthoquinone | : | Atovaquone |
| 11. | Antibiotics | : | Tetracycline; Doxycycline; Clindamycin |
| 12. | Sulfonamides/Sulphones | : | Sulfadoxime* |

* Combination is commonly used.

$ Combined with : Mefloquine, Amodiaquine, Pyrimethamine, Sulfadoxine

(a) Combined with : Lumefantrine

(b) Combined with : Piperaquine

**Anti-amoebic drugs**

- **Imidazoles**
  - Metronidazole
  - Tinidazole
  - Ornidazole
  - Satranidazole
  - Secnidazole
  - Nimorazole
- **Others**
  - Emetine, Dehydroemetine
  - Amide : Diloxanide (Furoate)
  - 8-Hydroxyquinolines : Iodoquinol
  - Antibiotics : Tetracycline; Paromomycin

## REVIEW QUESTIONS

**Long Answer Questions:**

1. Discuss DOTS therapy for tuberculosis.
2. Write mechanism of action, pharmacokinetics, adverse effects and drug interactions of INH.
3. Write mechanism of action, pharmacokinetics, adverse effects and drug interactions of Rifampicin.
4. Write mechanism of action, pharmacokinetics, adverse effects and drug interactions of Ethambutol.
5. Write mechanism of action, pharmacokinetics, adverse effects and drug interactions of Pyrazinamide.
6. Describe Revised National Tuberculosis Control Programme (RNTCP).
7. Classify leprosy and anti-leprotic drugs.
8. Discuss therapy of leprosy.
9. Classify clinically relevant types of fungi with examples.
10. Classify antifungal drugs.
11. Describe mechanism of action, pharmacokinetics, antifungal spectrum amd therapeutic uses and adverse effects of Amphotericin B.
12. Describe various azoles used for antifungal purpose.
13. Describe pharmacology of Flucytosine.
14. Describe pharmacology of Terbinafine.
15. Comment on topical antifungal drugs.
16. Which DNA viruses are clinically important?
17. Classify RNA viruses which are clinically important.
18. Describe various steps involved in replication of DNA viruses.
19. Describe various steps involved in replication of RNA viruses.
20. Classify antiviral drugs.
21. Describe mechanism of action, pharmacokinetics, antiviral spectrum and clinical use and adverse effects of Acyclovir.
22. Describe mechanism of action, pharmacokinetics, antiviral spectrum and clinical use and adverse effects of Ganciclovir.
23. Describe various steps involved in replicative cycle of HIV.
24. Classify antiHIV drugs with suitable examples.
25. Describe pharmacology of Zidovudine.
26. Describe combination therapy for HIV.

27. Classify clinically important helminths with suitable examples.
28. Comment on mechanism of action of various anthelmintic drugs.
29. Comment on choice of drugs for helminth infections.
30. Write pharmacology of Albendazole.
31. Write pharmacology of Mebendazole.
32. Describe pharmacological features of Diethylcarbamezine.
33. Describe pharmacological features of Praziquantel.
34. Describe pharmacological features of Pyrantel pamoate.
35. Describe pharmacological features of Ivermectin.
36. Describe life cycle of malarial parasite indicating sites of action for Antimalarial drugs.
37. Classify Antimalarial drugs with suitable examples based on chemical structure.
38. Classify Antimalarial drugs with suitable examples based on plasmodial state.
39. Classify Antimalarial drugs with suitable examples based on clinical use.
40. Write pharmacological features of Chloroquine.
41. Write pharmacological features of Quinine
42. Write pharmacological features of Primaquine.
43. Justify combination therapy for Antimalarial drugs.
44. Write pharmacological features of different Artemisinin derivatives.
45. Describe life cycle of amoeba indicating sites of action of Antiamoebic drugs.
46. Write pharmacological features of Metronidazole.

**Short Answer Questions:**

1. What is special about pharmacokinetics of Streptomycin?
2. What is major adverse effect of Streptomycin?
3. Which derivatives of Rifampicin are clinically useful?
4. Write a note on following drugs with respect to tuberculosis
   (a) Moxifloxacin (b) Amikacin
   (c) Capreomycin (d) Ethionamide
   (e) PAS (f) Cycloserine
   (g) Thiacetazone (h) Multidrug resistance (MDR)
   (i) Total drug resistance (TDR) (j) Hepatotoxicity
5. What is mechanism of action of INH?
6. What is mechanism of action of Rifampicin?
7. What is special adverse effect of Ethambutol?
8. What is use of Clofazimine in leprosy?
9. What is WHO regimen for leprosy?

10. Write short notes on following drugs

| | | | |
|---|---|---|---|
| (i) | Fluconazole | (ii) | Miconazole |
| (iii) | Itraconazole | (iv) | Valganciclovir |
| (v) | Penciclovir | (vi) | Famciclovir |
| (vii) | Vidarabine | (viii) | Cidofovir |
| (ix) | Adefovir | (x) | Entecavir |
| (xi) | Idoxuridine | (xii) | Trifluridine |
| (xiii) | Foscarnet | (xiv) | Ribavirin |
| (xv) | Fomivirsen | (xvi) | Amantadine |
| (xvii) | Oseltamivir | (xviii) | Stavudine |
| (xix) | Lamivudine | (xx) | Abacavir |
| (xxi) | Zalcitabine | (xxii) | Didanosine |
| (xxiii) | Nevirapine | (xxiv) | Efavirenz |
| (xxv) | Delavirdine | (xxvi) | Tenofovir |
| (xxvii) | Indinavir | (xxviii) | Nelfinavir |
| (xxix) | Ritonavir | (xxx) | Tipranavir |
| (xxxi) | Enfuvirtide | (xxxii) | Maraviroc |
| (xxxiii) | Raltegravir | (xxxiv) | Thiabendazole |
| (xxxiv) | Bithionol | (xxxv) | Triclabendazole |
| (xxxvi) | Levamisole | (xxxviii) | Metrifonate |
| (xxxix) | Niclosamide | (xxxx) | Oxmniquine |
| (xxxxi) | Piperazine | (xxxxii) | Amodiaquine |
| (xxxxiii) | Mefloquine | (xxxxiv) | Quinacrine |
| (xxxxv) | Proguanil | (xxxxvi) | Atovaquone |
| (xxxxvii) | Artemether | (xxxxviii) | Halofantrine |
| (xxxxix) | Tinidazole | (*l*) | Ornidazole |
| (*li*) | Satranidazole | (*lii*) | Secnidazole |
| (*liii*) | Nimorazole | (*liv*) | Emetine |
| (*lv*) | Diloxanide furoate | | |

11. What is mechanism of action of NRTIs?
12. What is mechanism of action of NNRTIs?
13. What is mechanism of action of NtRTIs?
14. What is mechanism of action of Saquinavir?
15. What are intestinal amoebicides?
16. What are extra-intestinal amoebicides?

*Unit* ...**4**

# CHEMOTHERAPY AND IMMUNOPHARMACOLOGY

Upon completion of this unit, the student should be able to:

- Understand chemotherapy of urinary tract infections.
- Understand chemotherapy of sexually transmitted diseases.
- Understand chemotherapy of malignant conditions.
- Understand pharmacological actions of immunostimulants.
- Understand pharmacological actions of immunosuppresants.
- Understand pharmacological actions of protein drugs.
- Understand pharmacological actions of monoclonal antibodies.
- Understand pharmacological actions of biosimilars.

## 4.1 URINARY TRACT INFECTIONS

Urinary tract infection (UTI) is a common disorder. For anatomical reasons, the female lower urinary tract is more susceptible to infection. UTI may present itself as either acute or chronic form.

**Acute Infections:**

Infection localised to the urethra and bladder, ie cysto-urethritis is termed as lower UTI. It causes increased frequency and urgency of micturition, dysuria and pain in perineum. Fever, chills and leukocytosis are generally absent. Such infections are generally self limiting. If the kidneys are also involved in infection, then it is termed as pyelonephritis or upper UTI. In this case, the patient may have pain, fever, chills and leukocytosis. Urine is loaded with pus cells. Urine culture is positive and shows significant bacteriuria. If it happens during pregnancy and puerperium or in patients on immunosuppressive drugs, then it may cause septicaemia.

Inadequately treated acute infections can lead to chronic pyelonephritis.

**Chronic Infections:**

Patients with chronic infection show polyuria, In addition, general loss of health and weight, anaemia and hypertension are frequently present. It is a common cause for hypertension and chronic renal failure. The urine may show pus cells. Significant bacteriuria is demonstrable.

Patients show fever and pyuria and may have bacterial invasion of kidney. In infants and children, UTI is difficult to detect. All urinary tract infections at this stage should be treated as pyelonephritis.

**Pathogenesis and Bacteriology:**

The bacteria commonly found in UTI originate in the rectum. From rectum, the organisms ascend to the urethra and bladder. The bacteria getting access to the bladder have following fate:

- They are washed out by emptying of the bladder.
- They are inhibited by acidic pH in urine, high urea content and hyperosmolarity of urine, or
- Destroyed by antibacterial action or the bladder mucosa.

Most of the urinary tract infections (95%) are due to Gram-negative bacteria like *E coli, Proteus mirabilis, Klebsiella, Aerobacter and Pseudomonas aeruginosa*. Remaining 5% may be *Enterococci, Streptococci and Staphylococci*. In chronic cases, mixed infections may be observed.

**Classification of Drugs:**

The drugs are classified in two major types: bacteriostatic agents and bactericidal agents. The examples of **bacteriostatic agents** are sulphonamides, tetracyclines and nitrofurantoin. The examples of **bacteriocidal agents** are Cotrimoxazole, Ampicillin, extended spectrum penicillins, Aminoglycosides, fluoroquinolones and cephalosporins. These drugs have been discussed earlier. Only comments relevant to UTI are included here.

**Urinary antiseptics** are the drugs which act as antibacterial agents only in urinary tract, eg Nitrofurantoin, Methenamine mandelate and Nalidixic acid.

**Individual Drugs**

**Sulphonamides:** They eradicate uncomplicated *E. coli* infections but are relatively ineffective in chronic cases, complicated cases or in mixed infections. Development of bacterial resistance is the major common problem.

A short acting sulphonamide like Sulfisoxazole should be administered in a dose of 2 gm initially, followed by 1 gm 6 hourly daily for 7-10 days. Urinary pH should be alkaline during therapy and fluid intake should be liberal. This initial treatment may be followed by 1 gm daily for several months as a chronic suppressive therapy. Cotrimoxazole is preferred over Sulfisoxazole.

**Tetracyclines:** They are particularly useful in non-gonococcal urethritis caused by *Chlamydia trachomatis*. Doxycycline is the drug of choice for acute urethral syndrome.

**Nitrofurantoin (Furadantin):** It is rapidly absorbed from GIT. Its urinary concentration is high but gives poor tissue levels due to extensive protein binding. Hence it is unsuitable for treatment of renal parenchymal infections. It is primarily bacteriostatic in nature against common urinary pathogens. Most strains of Pseudomonas and some strains of Proteus are resistant.

It is given in a dose of 50-100 mg/day and can be administered for several weeks as chronic suppressive therapy. It is mainly excreted by glomerular filtration and tubular secretion. Adequate urine levels are not obtained even on prolonged therapy in case of patients with kidney failure. Hence the drug should not be used in cases of severe renal insufficiency (creatinine clearance of 20 ml/min or less). It is mainly used in infections which are resistant to other more commonly used drugs. It exhibits therapeutic antagonism to Nalidixic acid. It has largely been replaced by other effective drugs.

**Methenamine Mandelate (Mandelamine):** It is a salt of Mandelic acid and methenamine, and combines antibacterial properties of both drugs.

It is rapidly absorbed from GIT and is excreted in urine. At an acidic pH less than 5.5, methenamine liberates formaldehyde which is active against many Gram-negative pathogens and *Candida albicans* causing UTI. Mandelic acid helps to lower urine pH.

It is not effective against upper urinary tract infections, Proteus and Pseudomonas species amnd acute infections. It has some value in chronic suppressive treatment when other drugs are not useful. It is used in a dose of 1 gm four times a day.

Larger doses may cause acute inflammation of UTI. Bacteria do not develop resistance to it. It should not be used along with Sulphamethizole; because the sulpha drug forms insoluble precipitate with formaldehyde.

**Nalidixic Acid:** Its dose is 4 gm/day in four divided doses for 7-10 days. It has no special advantage and is restricted for resistant Proteus.

**Cotrimoxazole:** It is a combination of Sulphamethoxazole and Trimethoprim. It is useful against *E coli and Proteus species* but not against *Pseudomonas*. It is used in a dose of 2 tablets twice a day for 7-10 days. In smaller doses of 1 tablet twice a week, it is useful for eliminating chronic bacteriuria. It should be avoided during pregnancy. It is less effective in renal insufficiency. Trimethoprim gets concentrated in the prostate; hence it is preferred when prostatic infection causes recurrent UTI.

**Penicillins:**

**Ampicillin** is bactericidal to *E coli, Aerobacter and* some strains of *Proteus*. It is ineffective against *Pseudomonas and* penicillinase-producing *Staph aureus*. It is used in a dose of 0.5 gm 6 hourly for 7-10 days. It is useful for treatment of UTI in pregnant women. Many strains of *E coli* exhibit resistance to it. Hence it is not the drug of choice.

**Carbenicillin** is useful in treatment of *Pseudomonas pyocyanea*, in which it is combined with Gentamycin. There is a caution that Carbenicillin and Gentamycin should be used in different syringes, because when combined in the same syringe, Carbenicillin inactivates Gentamycin.

**Piperacillin** has a broad spectrum of activity against Gram-negative organisms, especially, *Pseudomonas aeruginosa*. It is given IV in divided daily adult doses of 4-8 gm for moderate infections. The dose may be increased to 12-16 gms only in life threatening infections. It can be combined with Gentamycin for synergistic effects. Its use should be limited to severe UTI with life threatening septicaemia.

**Aminoglycosides:** Gentamycin and Amikacin are effective against *E. coli, Proteus and Pesudomonas*. These drugs can be given only parenterally. They can cause ototoxicity and renal toxicity. The nephrotoxicity can be reduced by giving entire daily dose at one time. Their use should be restricted to only complicated UTI.

**Fluoroquinolones:** They are preferred drugs for nosocomial pyelonephritis and complicating UTI. They are useful even if renal function is sub-normal. They are highly active at pH 5.5-6.0. The effective concentrations at acidic pH far exceed the bactericidal concentration for most pathogens.

**Cephalosporins:** These drugs are valuable in infections with *E coli and Proteus* resistant to other antibiotics. They are the drugs of choice in klebsiella infections. The newer cephalosporins are effective against multi-resistant enterobacteria and Pseudomonas resistant to other antibiotics. They are indicated in septicaemic UTI.

**Fosfomycin:** It has antibacterial action against urinary pathogens like *Ecoli, E fecalis, Klebsiella, P aeruginosa,* enterobacter, enterococci and staphylococci. Combination with Piperacillin/Cefotaxime acts synergistically against Gram-positive and Gram-negative organisms.

It inhibits bacterial cell wall synthesis by inactivating the enzyme pyruvyl transferase, which is critical in synthesis of cell walls by bacteria. It is bactericidal in nature.

It is well absorbed and achieves high concentrations in the urine. Protein binding is minimal. Its half-life is 4-8 hours. It is excreted unchanged in urine and high urinary levels, 100 µg/ml, persist for more than 8 hours.

Adverse reactions include headache, rash, diarrhoea, nausea, vomiting, abdominal discomfort, anorexia, dizziness, drowsiness, fatigue and pruritus. No dosage adjustment is required in hepatic impairment.

Antacids or calcium salts can decrease absorption of Fosfomycin. It is administered as a single dose of 3 gm in 100 ml of water. It is currently used for treatment of uncomplicated UTI in women.

## 4.2 SEXUALLY TRANSMITTED DISEASES (STDs)

Sexually transmitted diseases (STDs) are a group of infections most commonly transmitted by sexual contact. Accidental infection through fomites and infection of laboratory workers are rare modes of transmission. In case of syphilis, transplacental transmission to the foetus can occur.

The important STDs are syphilis, gonorrhoea, non-gonococcal urethritis, chancroid, lymphogranuloma venereum, granuloma inguinale, vaginitis and AIDS. Drugs for AIDS have been discussed under subsection anti-retroviral drugs of section 3.1.4. Other drugs are discussed below.

**Syphilis:**

Syphilis is caused by the spirochete named *Treponema pallidum*. Penicillin is the drug of choice during all stages of syphilis. Cure is possible in about 90% of cases. Resistance is yet not reported.

There are two stages of syphilis: Early syphilis and late syphilis. Early syphilis is the stage during first four years of acquisition. It is divided into two types: Infectious and latent. During infectious stage, the patient has highly contagious surface lesions. During late syphilis, no lesions are demonstrated anywhere in the body. However the patient is serologically positive for syphilis.

Late syphilis is observed after first four years. It includes late latent syphilis, late neurosyphilis, cardiovascular syphilis and gummatous syphilis involving various organs in the body.

**Treatment of Syphilis**

The spirochete is extremely sensitive to penicillin. Plasma concentrations as low as 0.03 unit/ml are spirocheticidal. The concentration must be continuously maintained for about 10 days in cases of early syphilis and about 14-20 days in cases with late syphilis. The drug is always administered parenterally. Following principles should be followed in the treatment:

- Before starting the treatment, the diagnosis must be established with certainty.
- Treated cases should be followed up for adequate period.
- It is necessary to trace and treat contacts.

Following are the recommendations for different stages of syphilis:

- Primary and secondary syphilis and latent syphilis of one year's duration.
  - Procaine penicillin 600,000 units IM daily for 8 days or
  - Benzathine penicillin 2.4 megaunits IM (1.2 megaunits in each buttock) in a single dose.
  - Patients who are allergic to penicillin should be treated with Tetracycline or Erythromycin 500 mg orally, 4 times a day, on empty stomach or with Doxycycline 100 mg twice a day for 15 days.
- Syphilis, except neurosyphilis, of more than one year's duration.
  - Procaine penicillin 600,000 IM daily for 15 days or
  - Benzathine penicillin 2.4 megaunits IM once a week for 3 weeks.
  - Patients allergic to penicillin should be treated with Tetracycline or Erythromycin 500 mg orally, 4 times a day, on empty stomach or with Doxycycline 100 mg twice a day for 30 days.

**Neurosyphilis:**

All patients with neurosyphilis are associated with changes in CSF. Penicillin G should be given intravenously in the dose of 12 megaunits daily in four divided doses for 12-14 days. Alternatively, Procaine penicillin in a dose of 2-4 million units IM once a day, together with Probenecid 500 mg daily, for 10 days should be given. In case if CSF abnormalities persist, treatment should be repeated.

**Pregnancy and Syphilis:** Syphilis detected during pregnancy should be treated with any of the regimens of penicillin described above. Patients allergic to penicillin should be treated with Erythromycin, **but not with Tetracycline**.

**Congenital Syphilis:** It is a completely preventable condition. Syphilis detected in infants and children can be treated by injecting Procaine penicillin in the dose of 100,000 units daily for 10 days. Interstitial keratitis, a common complication of congenital syphilis needs use of local or systemic corticosteroids.

**Adverse Reactions:**

There are two major adverse reactions: Allergy and Jarish-Herxheimer reaction.

Allergic reactions to penicillin are expressed as skin rashes, arthritis, serum sickness like syndrome, renal disturbances, haemopoietic disturbances, angioedema and anaphylaxis.

Jarish-Herxheimer reaction is due to a rapid destruction of a large number of spirochetes with a release of endotoxin aggravating local inflammatory lesion. It leads to an aggravation of the mucocutaneous lesions and a mild systemic illness consisting of malaise, tachycardia and fever. It lasts for 2-6 hours and is harmless. In cardiovascular and neurosyphilis, Jarish-Herxheimer reaction may precipitate severe angina or CHF; and psychosis, convulsions, coma or optic atrophy.

**Gonorrhoea:**

It is caused by gonococci, most strains of which are sensitive to penicillin. Some strains are resistant to penicillin, tetracycline, or to spectinomycin and/or others. Eradication of acute, uncomplicated gonococcal infection caused by penicillin-sensitive organisms is easy. In case of resistant organisms, eradication is difficult.

Gonococcal infection is more difficult to diagnose and treat in females than in males. Further, acute pelvic inflammatory disease (PID) may be caused by other organisms like *Chlamydia trachomatis, Mycoplasma hominis,* vaginal flora including anaerobes, Gram-negative organisms like *E coli and* group B streptococci along with gonococci. In such cases, treatment of acute PID should be undertaken with multiple drugs covering all pathogens.

The antimicrobial regimen for uncomplicated and complicated gonorrhoea is mentioned below:

**Regimen for Uncomplicated Gonorrhoea:**

- Penicillin G, in aqueous form, 4.8 mega units injected in two divided doses, 30 minutes after 1 gm of oral Probenecid. It may be repeated if necessary.
- Ampicillin 3.5 gm orally, a single dose preceeded by 1 gm of oral Probenecid.
- Procaine penicillin 1.2 mega units along with penicillin G 1 mega units IM, followed by two similar injections 24 hours apart.
- Cotrimoxazole 2 tablets twice daily for 5 days, or 4 tablets twice daily for 2 days.
- Ciprofloxacin 500 mg orally as a single dose.
- Ceftriaxone 125-250 mg, IM as a single dose.

- Cefixime 400 mg orally as a single dose.
- Spectinomycin 2 gm IM as a single dose.

**Regimen for Complicated Gonorrhoea:**

- Procaine penicillin 2 mega units daily for 10 days along with Tetracycline 500 mg QID or Doxycycline 100 mg BID for 14 days.
- Cefoxitin IV 2 gm every 6 hours along with Doxycycline IV 100 mg every 12 hours. Continue the treatment for 48 hours. After substantial improvement, continue Doxycycline orally 100 mg BID for 14 days.
- Gentamycin IV or IM, in a loading dose of 2 mg/Kg followed by 1.5 mg/Kg for every 8 hours in patients with normal renal function. In addition, Clindamycin 900 mg IV is given every 8 hours. After clinical improvement, change over to Doxycycline 100 mg 12 hourly, to complete 14 days of total treatment.
- Ofloxacin orally 400 mg BID for 14 days along with Clindamycin orally 450 mg QID for 14 days or Metronidazole orally 500 mg BID for 14 days. This regimen may be useful even in non-hospitalised patients.

All patients of gonorrhoea should be investigated regularly and frequently for the development of positive serological tests for syphilis. If observed to be infected with syphilis, dose of penicillin should be given.

**Non-Gonococcal Urethritis (NGU)**

NGU may be due to one of the following reasons:

- Infection with *Trichomonas vaginalis.*
- A generalised UTI.
- Non-specific urethritis: In half the cases, infect ion with *Chlamydia trichomatitis* is the cause. The patients complain of dysuria and a variable amount of urethral discharge. The disease shows frequent recurrence. The treatment choice is Doxycycline 100 mg twice a day or Tetracycline 500 mg 6 hourly, for 7-14 days. Erythromycin 500 mg 6 hourly for 7 days can also be an alternative. Another alternative is Azithromycin in a single dose of 1 gm; it is safe in pregnancy. The sexual partner should be treated at the same time to prevent reinfection.

**Chancroid:**

It is caused by *H ducrei.* The treatment is Erythromycin 500 mg orally four times a day for 7-10 days. Azithromycin in a single dose of 1 gm is also effective. Alternative regimens are Cotrimoxazole 2 tablets twice a day for 7 days; Ciprofloxacin 500 mg orally twice a day for 3 days; and Ceftriaxone 250 mg IM as a single dose. Ampicillin and Tetracycline should be avoided for the fear of resistance.

**Lymphogranuloma Venereum**

It is caused by Chlamydia. The treatment is Tetracycline 500 mg 6 hourly or Doxycycline 100 mg twice a day for 21 days. In chronic hypertrophic type, surgery may be needed in addition to tetracyclines for 6-8 weeks. Sulphonamides are equally effective. Erythromycin may also be used.

**Granuloma Inguinale:**

It is caused by *Donovania granulomates*. It responds well to Tetracycline, Sulphisoxazole or Ampicillin orally in a dose of 500 mg 6 hourly for 3-4 weeks; and Cotrimoxazole two tablets twice daily for the same duration.

**Veneral warts:**

It is due to a viral infection (Condylomata accuminata) without any systemic effects. It causes warts, which grow rapidly in the presence of moisture and are inhibited by dryness. They are treated either by electric cautery under local anaesthesia or by applying podophyllum resin (20% suspension in liquid paraffin or alcohol) or trichloroacetic acid. The surrounding skin should be protected from podophyllum. Imiquimod 5% cream applied three times a week is useful. It acts by inducing local production of interferon α alone with pro-inflammatory cytokines named Interleukines 1,6 and 8 and TNFα

**Vaginitis:**

It is a common condition caused by three types of organisms: *Candida albicans* (yeast), *Trichomonas vaginalis* (trichomonas) and *Gardenella vaginale* (bacteria).

Candida vaginitis responds to intra-vaginal therapy with triazoles, once each night for 3-7 days. A single oral dose, 150 mg of Fluconazole is as effective as several days of Clotrimazole and Miconazole locally. Metronidazole is the drug of choice for trichomoniasis. Bacterial vaginitis also responds to Metronidazole 500 mg bid for 7 days. Alternatively, Clindamycin may be used. Similar regimens should be used to treat male partners, because 90% of them are carriers of *G vaginale*. Systemic treatment should be preferred over local application.

Single dose regimen for various STDs is presented in Table 4.1.

**Table 4.1 : Single dose regimen for STDs**

| Sr. No. | Infection | Treatment |
|---|---|---|
| 1. | Syphilis (early) | Benzathine penicillin as IM injection. |
| 2. | Gonorrhoea | See treatment of uncomplicated gonorrhoea. |
| 3. | Chlamydial NGU | Azithromycin 1 gm orally. |
| 4. | Chancroid | Azithromycin 1 gm/Ciprofloxacin 500 mg orally or Ceftriaxone 250 mg IM. |
| 5. | Trichomoniasis | Metronidazole 2 gm orally. |

Single dose regimen is not recommended for lymphogranuloma venereum and granuloma inguinale.

AIDS is also a STD. Therapy of AIDS is discussed under antiviral drugs.

## 4.3 CHEMOTHERAPY OF MALIGNANCY

Cancer refers to a disease of cells which shows uncontrolled proliferation, dedifferentiation i.e. anaplasia, invasiveness and the ability to metastasise i.e. spread to distal parts of the body. The appearance of abnormal characteristics refers to chromosomal abnormality including an expression of abnormal gene sequences, called as oncogenes. When such cells proliferate excessively, they form local tumours which can invade surrounding normal cellular structures. The extent of metastasis and deterioration in metabolic processes, resulting from cancer, leads to death of the patient, unless the neoplasm is successfully eradicated by the treatment.

There are four main approaches to treat cancer:

1. Surgical resection.
2. Radiotherapy.
3. Chemotherapy.
4. Immunotherapy ie use of monoclonal antibodies.

Out of these four approaches, chemotherapy will be discussed here.

**Types of Cancer:**

Tumours are of two types: benign and malignant. Benign tumours are generally slow growing, resemble normal cells, remain localised and are usually not harmful. The terms like cancer/malignant neoplasm/malignant tumour are synonymous. They proliferate rapidly, manifest dedifferentiation, invasiveness and the ability to metastasise. They inflict damage on the surrounding cells and are harmful if untreated.

Benign tumours are usually ending with the term "oma". Thus papilloma means cancer of surface epithelium, adenoma means cancer of glandular epithelium, melanoma means cancer of pigment cells, myoma refers to muscle tissue, fibroma refers to fibrous tissue and neurofibroma refers to cancer of nerve cells.

Malignant cancers are divided into solid tumours and haematological malignancies. Solid tumours can be carcinomas, adenocarcinomas, sarcomas or myelomas. Haematological malignancies include lymphoma and leukaemia.

**Causes of Cancer:**

Following factors are related to causes of cancer:

- Viruses like Epstein-Barr virus (EBB), Hepatitis-B virus (HBV) and Human Papilloma virus (HPV).
- Environmental and occupational hazards like radiation or chemicals.
- Diet and habits like high fat and low fibre, tobacco and/or alcohol consumption.
- Genetic factors like mutations, expression of oncogenes and repression of tumour suppressor genes.
- Use of drugs like immunosuppressives and some alkylyting agents.

Two types of genetic changes lead to cancer. One is activation of proto-oncogenes to oncogenes. The other is repression or inactivation of tumour suppressor genes (antioncogenes).

**Characteristics of Cancer Cells:**

There are four characteristics of cancer cells: Uncontrolled proliferation, dedifferentiation, invasiveness and metastasis. They are discussed below.

**Uncontrolled Proliferation:** The genetic changes in cancerous cells confer autonomy of growth to them, so that their proliferation is subject to normal physiological processes. The factors are as follows:

**Growth factors:** Growth factors like Epidermal Growth factor (EGF), Insulin-like Growth Factor (IGF), Platelet Derived Growth Factor (PDGF), Transforming Growth Factor-β (TGF-β) and Vascular Endothelial Growth Factor (VEGF) and their respective receptors eg EGRF, IGFR, PDGFR and VEGFR. Growth factors act through receptor tyrosine kinase or receptor-coupled other kinases.

**Cell cycle transducers:** They are of two types: positive regulators and negative regulators. Positive regulators belong to two families: cyclines and cycline-dependent kinases (CDKs). Negative regulators include Rb proteins, protein p21, other CDK inhibitory proteins (CIP family) and inhibitors of kinases (Ink family).

**Apoptosis:** Apoptosis means programmed cell death. It prevents cancer by monitoring the cancerous changes. The apoptosis can take place by two pathways: death receptor pathway, which stimulates tumour necrosis factor (TNF) or mitochondrial pathway which activates the enzyme caspase-9.

**Angiogenesis:** It influences the total tumour mass through the action of VEGF, produced by growing tumour.

**Telomerase expression:** Telomers are the protective caps over ther distal extremity of a chromosomal arm. They are long in cancerous cells and short in normal cells. Many malignant tumours express an enzyme telomerase which provides immortality to cancer cells. Inhibitors of telomerase enzyme can work as anticancer drugs.

**Dedifferentiation:** Normally, when daughter cells are matured, they differentiate and behave like their parent cells; eg muscle cells will start contracting. However cancer cells do not differentiate. As a result they grow in an uncontrolled manner with the same morphology.

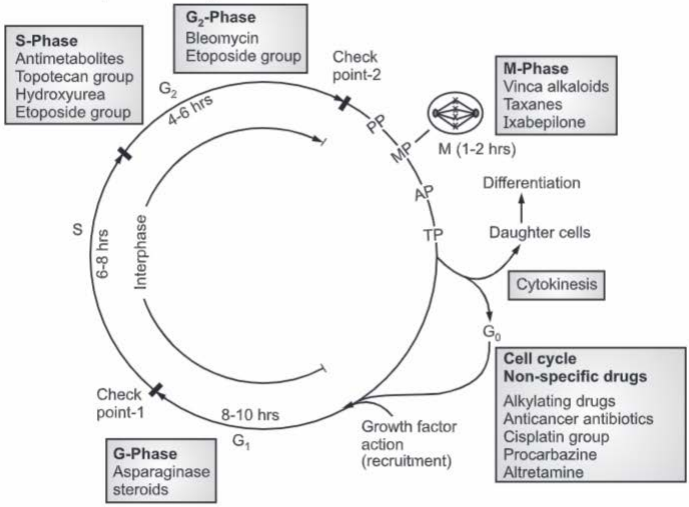
**Invasiveness:** Normal cells are not found outside their tissue of origin, eg. cardiac cells are not found in brain. If any cell accidentally escapes, it would undergo apoptosis and die. The cancer cells, due to mutations, have no such limitation and can slip into nearby organs.

**Metastasis:** Cancer cells can disseminate to distal organs through blood and lymphatics, eg. bone cells can metastasise into lungs. It can lead to spread of cancer throughout the body.

**The Cell Cycle:**

The cells reproduce themselves through cell division. The division is of two types: mitosis and meiosis. During mitosis, each daughter cell gets the same number and kind of chromosomes as that of parent cell. During meiosis, the daughter cells contain half the number of chromosomes. The normal cells are termed as diploid cells containing 2n number of chromosomes. During mitosis the number 2n of chromosomes is retained. During meiosis, dipoloid cells are converted to haploid cells, containing n number of chromosomes. During meiosis, sperms and egg cells are generated. The cells grow in different phases as mentioned below.

**Phases of Cell Cycle:** Following are the phases of cell cycle: $G_0$ phase, $G_1$ phase, S phase, $G_2$ phase and M phase. See Fig. 4.1.




Key: PP-Prophase; MP-Metaphase; AP-Anaphase; and TP-Telophase

**Fig. 4.1**

**$G_0$ phase:** Most cells do not divide constantly and spend a varying amount of quiescent/calm state outside the cell cycle. This phase is called as $G_0$ phase. Neurons, skeletal muscles and cardiac muscles spend most of their life time in $G_0$ state; indicating lack of division. On the contrary, bone marrow cells, GIT cells and skin cells divide constantly and pass through different stages as mentioned below. The growth factors provide momentum for the beginning of the cell cycle. See Fig. 4.1. The cell cycle consists of two major activities: The interphase i.e. $G_1 \rightarrow S \rightarrow G_2$ phase; and the cell division ie mitosis, M phase and cytokinesis.

**Interphase:** When the cell is in between one mitosis and the next, it is said to be in interphase. It is during interphase that the replication of chromosomes happens. In addition, DNA, RNAs and protein, needed to produce structures which are required for doubling all cellular components are manufactured in this phase. Interphase consists of three distinct phases: $G_1$, S and $G_2$ phase.

**$G_1$, S and $G_2$ phases:** It is a growth or gap phase during which cells are engaged in metabolism and production of substances required for forthcoming cell division and growth. In **S** (synthesis) phase, DNA and chromosomes are replicated. S phase is followed by another growth phase, **$G_2$** phase. It is a gap period between S phase and mitosis. During $G_2$ phase, the cell prepares itself for mitotic division into two daughter cells. In $G_1$ and $G_2$ phase there are no events related to chromosomal or DNA replication. These phases simply serve as preparatory ground or gaps in DNA synthesis.

Some cells like nerve cells, skeletal muscle cells are permanently arrested in $G_1$ phase; but once a cell enters S phase it is bound to go through mitosis ie M phase. An entry of the cell into the S phase or M phase is controlled at two check points in the cell cycle. See Fig. 4.1. One check point starts at the beginning of S phase and another check point starts at the beginning of M phase. In the quiescent $G_0$ phase, a specialised protein called Rb protein is not phosphorylated. Bare Rb protein serves as a break keeping the cells in the $G_1$ phase by inhibiting the genes essential for passing into S phase. In mid $G_1$, the cyclin-cdk complex phosphorylates the Rb protein to release this break ie check point 1. If there is DNA damage, the tumour suppressor gene named p53 stops the cycle at check point 1, allowing the physiological repair. Once check point 1 is cleared, the process cannot be reversed and the cell enters S phase. Any abnormal DNA synthesis or DNA damage in S phase or $G_2$ phase can further stop the cell cycle at check point 2 by inhibiting the formation of cyclin B-cdk 1 complex.

**Mitosis (M phase):** It can be divided further into four stages: prophase, metaphase, anaphase and telophase. They are discussed below.

1. **Prophase (pro means before) PP:** Till now, the chromosomes, although duplicated, are in a form of tangled mass filled inside the nucleus. In prophase, they condense into visible chromosomes ie two sister chromatids joined at centromere. Nuclear membrane now disintegrates and condensed chromosomes are released in cytoplasm.
2. **Metaphase (meta means after) MP:** During metaphase, the centromeres of the chromatid pair, collectively a chromosome and its copy, line up at the exact centre of the mitotic spindle in an equatorial plane. See figure 4.1.
3. **Anaphase (ana means upward) AP:** During anaphase, centromeres divide and identical sets of chromosomes move to the opposite poles of the cell. The separated sister chromatids are referred to as daughter chromosomes.

4. **Telophase (telo means at the end) TP:** Telophase is the end stage of mitosis and is opposite to that of prophase. During this stage, the identical sets of chromosomes at opposite poles of the cell uncoil and revert to their thread-like chromatin form. A new nuclear envelope is re-formed around chromatin mass. Nucleoli reappear and the spindle disappears.

**Cytokines or Cytoplasmic Division:** During this stage, a division of parental cytoplasm and organelles take place. A cleavage furrow is formed around the centre of the cell, which gradually deepens and separates the cytoplasm and the organelles into two equal and different portions. The separated two daughter cells now have equal and separate portion of cytoplasm, organelles and its own set of identical chromosomes. The daughter cells may now undergo differentiation or remain in $G_0$ phase, or if stimulated, may enter into interphase ($G_1$-S-$G_2$), mitosis (M phase) and cytokinesis.

**Length of Cell Cycle:** The length of $G_1$ phase of cell cycle is highly variable. Normally, it takes about 8-10 hours, but it may be even non-existent in rapidly dividing cells. It may take even days, weeks or years in some other types of cells. Usually, the S phase takes about 6-8 hours; $G_2$ phase about 4-6 hours and mitosis and cytokinesis about 1-2 hours. Together, the various phases of cell cycle require about 18-24 hours in mammalian cells.

**Sites of Anticancer Drugs:** Anticancer drugs may be broadly classified according to their cell cycle cytotoxic effects. See figure 4.1. Combination of chemotherapeutic agents which are active in different phases of cell cycle can result in a greater cell kill. Anticancer drugs falling into cell cycle-specific and cell cycle-non-specific category are mentioned in the next section related to classification. Drugs which are cytotoxic to the cells non-selectively at any point in the cycle are called as **"cell cycle-non-specific drugs",** while **"the cell cycle-specific drugs"** exhibit phase selectivity; either at $G_1$ or S or $G_2$ or M-phase.

**Classification of Anticancer Drugs:**

- Alkylating agents: eg Busulfan, Carmustine, Lomustine, Bendamustine, Chlorambucil, Cyclophosphamide, Melphalan, Decarbazine, Mechlorethamine-Ifosfamide, Thiotepa, Temozoiomide, Sterptozotocin and Estramustine.
- Antimetabolites: eg Methotrexate, Pemetrexed (folic acid analogues), Thioguanine, Mercaptopurine, Fludarabine, Pentostatin, Cladribine, Nelarabine, Clofarabine (purine analogues), Cytarabine, Fluorouracil, Floxuridine, Gemcitabine and Capecitabine (pyrimidine analogues).
- Antibiotics: eg Bleomycin, Dactinomycin, Mitomycin-C, Daunorubicin, Idarubicin, Doxorubicin, Epirubicin and Mitoxantrone.
- Natural products: eg Vincristine, Vinblastine, Vinorelbine (vinca alkaloids), Etoposide, Teniposide (epipodophyllo toxins), Topotacan, Irinotecan (camptothecins), Paclitaxel, Docetaxel, Ixabepilone (taxanes), L-Asperginase (enzyme).
- Miscellaneous agents: eg Hydroxyurea, Cisplatin, Carboplatin, Oxaliplatin, Procarbazine, Hexamethylmelamine (HMM/ Altretamine), Arsenic trioxide, Tretinoin, Bexarotene, Denileukin diftitox, Thalidomide, Lenolidomide.

- Protein Tyrosine Kinase Inhibitors: eg Imatinib, Dasatinib, Nilotinib, Lapatinib.
- Epidermal Growth Factor Receptor (EGFR) Inhibitors: eg Gefitinib, Sorafenib, Sunitinib, Erlotinib.
- Proteosome inhibitors: eg Bortezomib.
- Hormones and antagonists eg:
  - Gn-RH agonists: Goserelin, Buserelin, Leuprolide.
  - Gn-RH antagonists: Cetorelix, Ganirelix, Abarelix.
  - Corticosteroids: Dexamethasone, Prednisolone.
  - Adrenocortical suppressants: Aminogluthemide, Trilostane.
  - Aromatase inhibitors: Anastrozole, Letrozole, Exemestane.
  - Estrogen receptor antagonists(ERA): Tamoxifen, Toremifen, Fulvestrant.
  - Androgen receptor blockers: Flutamide, Bicalutamide, Nilutamide.
  - Progestins: Hydroxyprogesterone, Medroxyprogesterone, Megestrol acetate.
  - Estrogens: Diethylstilbestrol, Ethynyl estradiol.
  - Androgens: Testosterone propionate, Fluoxymesterone.
- Monoclonal antibodies eg:
  - Naked MAbs: Rituximab, Epratuzumab, Alemtuzumab, Trastuzumab, Cetuximab, Panitumumab, Bevacizumab, Edrecolomab.
  - MAbs-cytotoxic conjugates: Gemtuzumab ozogamicin.
  - Radioisotope-based MAbs: Ebritumomab-$^{90}$Y, Tostitumomab-$^{131}$I.
- Histone Deacetylase (HDAC) Inhibitors: eg Vorinostat.
- Protectants eg:
  - Colony stimulating factors: Filgrastim, Sargamostim.
  - Thiophosphate cytoprotectants: Amifostine.
  - Acrolein conjugator: Mesna.
  - Iron chelator: Dexrazoxane.
  - Thrombopoietic growth factors: Oprelvekin (IL-11), Thrombopoietin.
  - Others: Levamisole

Another classification is based on existence of two major classes: Antimetabolites and monoclonal antibodies. Out of these two types antimetabolites are further sub-classified into three major types: Folic acid analogues, purine analogues and pyrimidine analogues. Monoclonal antibodies (MAbs) are a common class to both the types of classifications. Information about antimetabolites and MAbs is presented below.

See Fig. 4.2 to emphasise sites of actions of anticancer drugs.

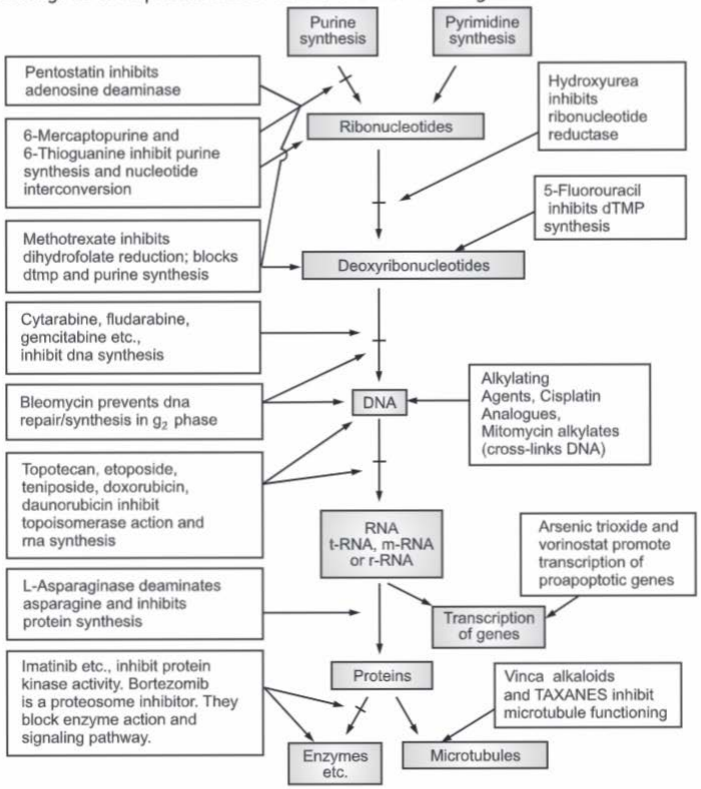



**Fig. 4.2: Sites of action of anticancer drugs**

**Drugs used for Cancer Chemotherapy:**

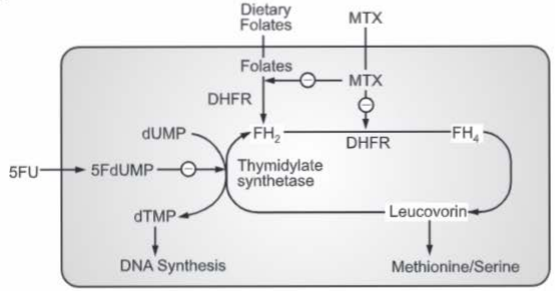
Antimetabolites are sub-classified in three types: Folic acid analogues, purine analogues and pyrimidine analogues. They are described below.

**Antimetabolites**

**Folic acid Analogues:**

The example in this category is Methotrexate. By competitively inhibiting the dihydrofolate reductase enzyme, Methotrexate deprives the cancer cells of various folate

coenzymes and essential components of DNA like purines, methionine and thymidine monophosphate (dTMP), leading to cell death. See Figure 4.3. The cells in S- phase are more sensitive to the cytotoxic effects of Methotrexate. See figure 4.1. The RNA and protein synthesis is also inhibited to some extent. As a result, the progression of cell cycle from $G_1$-to S-phase is also delayed. Administration of Leucovorin (folinic acid) rescues normal cell from toxicity of Methotrexate.




Key: $FH_2$ - Dihydrofolic acid; $FH_4$ - Tetra hydrofolic acid; DHFR-Dihydrofolate reductase; dUMP-Deoxyuridine monophosphate; dTMP-Deoxythymidine monophosphate

**Fig. 4.3**

**Purine Analogues:**

The examples in this category are: 6-Mercaptopurine (6-MP), Thioguanine (6-TG), Fludarabine, Cladribine and Pentostatin.

**6-Mercaptopurine** is an analogue of hypoxanthine. After penetrating the target cells, it gets converted into a false nucleotide. Resulting false DNA nucleotides are non-functional. Allopurinol, being xanthine oxidase inhibitor, prevents metabolism of 6-MP leading to an increase in its plasma concentration which causes toxicity of 6-MP.

**Thioguanine** is another purine analogue. It is not metabolised by xanthine oxidase. Hence Allopurinol does not potentiate its toxicity. It also leads to formation of a false transmitter.

**Fludarabine** is a fluorinated purine analogue of antiviral drug Vidarabine. It is converted to an active metabolite-a triphosphate derivative which interferes with DNA synthesis.

**Cladribine** is a synthetic purine nucleoside which is phosphorylated to an active metabolite which exhibits a cytotoxic action by fraudulent incorporation into DNA.

**Pentostatin** is a purine analogue obtained from *Streptomyces antibioticus*. It inhibits the enzyme adenosine deaminase which plays a critical role in purine utilisation and DNA synthesis. The enzyme adenosine deaminase converts adenosine to inosine and its inhibition leads to an inhibition of methylation and other reactions.

**Pyrimidine Analogues:**

The examples in this category are: Cytarabine, 5-Fluorouracil (5-FU) and Floxuridine, Capecitabine, Gemcitabine.

**Cyterabine** is an analogue of deoxy-cytidine which inhibits DNA synthesis by inhibiting the enzyme DNA polymerase. It also gets incorporated into DNA which results in formation of fraudulent DNA.

**5-Fluorouracil (5-FU) and Floxuridine** are fluorinated pyrimidines. Their active metabolite inhibits the enzyme thymidylate synthetase (TS). Inhibition of this enzyme leads to derangement in the synthesis of dTMP. It results into inhibition of DNA synthesis due to depletion of thymine. 5-FU is also phosphorylated and leads to formation of fraudulent RNA. Concurrent administration of Leucovorin enhances action of 5-FU by facilitating inhibition of enzyme TS.

**Capecitabine** is a fluoro-pyrimidine carbamate. It is a prodrug which gets converted into an active metabolite. Its mechanism of action resembles the action of 5-FU.

**Gemcitabine** is a difluorodeoxycytidine, which is an analogue of nucleoside deoxycytidine. It serves as a substrate for an enzyme deoxycuytidine kinase. The resultant product inhibits DNA synthesis and repair by incorporating into DNA fraudulently.

**Monoclonal antibodies (MAbs):**

MAbs are single species of antibody which recognise and react with a specific antigen only. They are produced by cloning of hybrid cells created by fusing an immortal cell from mouse myeloma with a B-cell producing antibody against a desired antigen. The resulting hybridomas have an ability of B-lymphocytes to secrete a single species of antibody and the capability of cancer cells to proliferate endlessly. They exert cytotoxic action and facilitate apoptosis.

Murine MAbs, generated from rodents like mouse are usually not preferred since they have a shorter half- life and induce a human antimouse-antibody allergic response. Hence a chimerised MAbs are commonly used; the word chimerised indicates partly human and partly mouse MAbs. The names of chimeric MAbs usually end up with "ximab" (eg Rituximab) while those of humanised MAbs end up with "Umab" (eg Trastuzumab).

Some monoclonal antibodies are used as anticancer drugs.

**Adverse Reactions:**

Chemotherapeutic agents used to treat cancer are most toxic to rapidly proliferating cells like mucus membranes, skin, hair, GIT and bone marrow. As a result anticancer agents show widespread toxicity which can even be life threatening. The types of adverse reactions are listed below.

- Bone marrow suppression
- Dermatological toxicity
- GIT toxicity
- Neurotoxicity

- Renal toxicity
- Haemorrhagic cystitis
- Hepatotoxicity
- Cardiotoxicity
- Pulmonary toxicity
- Infertility
- Hypersensitivity reactions
- Tumour Lysis Syndrome (TLS)
- Miscellaneous

**Resistance to Anticancer Drugs:**

Cancers can be regarded as population of cells undergoing spontaneous mutations and as the tumour grows, increasing number of mutations occurs. Some tumour types, like malignant melanoma, brain cancer and renal cell cancer, exhibit primary resistance i.e. absence of response to standard drugs right from the first exposure. On the contrarary, some cells show acquired resistance, which develops during continuation of therapy. Primary resistance is associated with the inherent genomic instability, while acquired resistance may result from either adaptation of tumour cells or due to mutation with amplification or increased expression of one or more specific genes. Tumours which are resistant to drugs will always have largely drug- resistant population which are refractory to the treatment. Combination therapy may be useful in resistant cells.

**Combination Therapy:**

The combined use of two or more anticancer drugs is often superior to a single drug therapy in most of the cancers. Following are the principles used for combination therapy:

- Each drug used in combination should have individual therapeutic activity against the tumour.
- The combined regimen should include drugs which act by different mechanisms. Such combinations are usually synergistic.
- Drugs having different dose- limiting toxicities should be selected to avoid cumulative damage to a single organ.
- In order to allow time for recovery from acute toxic effects of cytotoxic drugs, intermettant schedule of drug treatment should be opted. One or two cycles of chemotherapy are hardly sufficient to eradicate a tumour. Hence based on clinical response, 4-6 cycles may be repeated.
- If the primary tumour has been eradicated either with surgery or radiation, then adjuvant chemotherapy should be given to decrease the chances of relapse. It gives good results in breast cancer, colorectal cancer, prostate cancer and osteosarcoma.
- A large number of combination regimens are used for treating various types of cancers.

## 4.4 IMMUNOPHARMACOLOGY

Drugs which modify immune responses are termed as immunomodulators. They can function either to stimulate the immunity or to suppress the immunity. Accordingly they are termed as immunostimulants or immunosuppressants. They are discussed below.

### 4.4.1 Immunostimulants

There are various disorders like Acquired Immuno-Deficiency Syndrome (AIDS), autoimmune disease, cancer and viral infections which need use of immunostimulant drugs. These drugs are non-specific and may affect innate as well as adaptive immunity. They may work on cellular or humoral immune system or both. Because of their variable effects, they are popularly known as biological response modifiers or Immunomodulators.

Some of them are synthetic drugs like Levamisole, Thalidomide and Lenalidomide. One of them is a live bacterial culture. Some of them are recombinanat cytokines or interferons. They are discussed below:

**Bacillus Calmette-Guerin (BCG):** BCG is an attenuated live culture of Calmette-Guerin strain of bacillus *Mycobacterium bovis*. Its active constituent is muramyl dipeptide. Its action is non-specific and stimulates T-cells and NK cells. It is also used for the treatment of urinary bladder cancer where it is instilled and held for 2 hours before urination. It is also used to boost active immunity towards tuberculosis. Common adverse effects include chills, fever, malaise, hypersensitivity reactions and shock.

**Levamisole:** It is an antihelminth drug but stimulates T-cell functions and B cells monocyte and macrophage activity. The action on T cells is predominant. It is combined with 5-fluorouracil to improve survival of patients suffering from colorectal cancer. It is also claimed to be useful in vitiligo in a dose of 150 mg OD orally for two consecutive days in a week for 3-4 months. Adverse effects include flu like symptoms, allergic manifestation, nausea and muscle pain.

**Thalidomide and Lenalidomide:** Thalidomide is available for restricted use i.e. to treat erythema nodosum leprosum and multiple myeloma because of its immunomodulatory and anti-inflammatory effects. It decreases TNF-α levels in blood and produces anti-angiogenic effects. Hence it is indicated in refractory cases of rheumatoid arthritis and in certain malignancies. Because of its teratogenecity, it is contraindicated in pregnancy.

Lenalidomide is an analogue of Thalidomide with immunomodulatory and anti-angiogenic properties. It is used for treatment of transfusion-dependent anaemia due to myelodyspastic syndrome. Its adverse effects include neutropenia, thrombocytopenia, risk of deep vein thrombosis and teratogenecity. It is contraindicated in pregnancy.

**Recombinant Cytokines:** There are three types of cytokines used as immunostimulants. They are as follows:

**1. Aldesleukin:** These are recombinant IL-2 obtained from cultures of *E coli.* It stimulates TH cells and Tc cells leading to enhancement of cellular immunity. It is used in the treatment of metastatic renal cell carcinoma and melanoma. Adverse effects include capillary leak syndrome, hypotension, reduced tissue perfusion and concomitant infection due to decrease in neutrophil function.

**2. Other recombinant interleukins (rIL):** rIL-1 is produced by macrophages and is essential for activation and proliferation of various immune cells. It is given intravenously for general augmentation of immune response. It stimulates megakaryocytes and their precursors in the bone marrow. It is used to prevent thrombocytopenia in the patients of cancer receiving highly myelosuppressive chemotherapy.

**3. Colony stimulating factors (CSFs):** Recombinant GM-CSF like Sargramostin, G-CSF like Filgrastim and pegylated recombinant G-CSF like Pegfilgrastim are some of the important cytokines used for survival-proliferation and differentiation of haemopoietic cells. Sargramostin is multipotent haemopoietic growth factor affecting granulocytes, erythroids, megakaryocytes and macrophages. Filgrastim stimulates proliferation and differentiation of neutrophil progenitor cells, activates the phagocytic activity of mature neutrophils and prolongs their survival in circulation. Pegfilgrastim is a long acting analogue of Filgrastim and can be given once intravenously per chemotherapy cycle. All CSFs are used to reduce the severity and duration of neutropenia induced by cytotoxic drugs during chemotherapy or following bone marrow transplant.

**Recombinant Interferons:**

Interferon-α (IFN-α) is a human recombinant interferon and acts as an immunostimulant. It activates T lymphocytes, natural killer cells (NK) and macrophages. Both IFN-α and IFN-α2b are indicated for a variety of cancers like chronic myeloid leukaemia, hairy cell leukaemia, malignant melanoma, non-Hodgkin's lymphomas and AIDS-related Kaposi's sarcoma. IFN-α is additionally used in the treatment of hepatitis B and C virus infections. Adverse effects include flu-like syndrome, blood dyscrasias, nephrotoxicity and neurological symptoms like nervousness and confusion.

Interferon-β1a and β1b are used for the treatment of relapsing type multiple sclerosis. Adverse effects include flu-like symptoms and local reactions at the injection site.

Interferon-Y, mainly IFN-Y1b, restores macrophages cytotoxicity by generating free radicals and is used for the treatment of chronic granulomatous disease. Adverse effects include flu-like symptoms, GIT distress, anorexia and skin rashes.

**Preparations:**

- Bacillus Calmette-Guerin: BCG (strain $1X10^6$ and $33X10^6$ CFU) vial injection.
- Levamisole: 50 mg, 150 mg tab, 50 mg/5 ml syrup: **Dewormis, Dicaris, Vermisol.**
- Filgrastim: 300 µg pre-filled syringe injection: **Filgen, Grafeel.**
- Interferon α2a: 3 Mu/vial injection: **Alferon.**
- Interferon α2b: 3 mU/vial, 5 mU/vial injection: **Shanferon, Viraferon.**

### 4.4.2 Immunosuppressants

These drugs are classified under following sections:

1. Inhibitors of lymphocyte gene expression to reduce inflammatory response: **Glucocorticoids**.

Inflammatory response can be reduced by inhibition of lymphocyte gene expression. Glucocorticoids suppress the initiation and generation of a fresh immune response more effectively. Local regulation of cytokine release, from T cells, stimulates leukocyte recruitment and activation. Glucocorticoids inhibit cytokine synthesis and release, eg IL-1, IL-2, IL-6 and TNF-α is affected. This suppresses immune responses by inhibiting the activation of cytotoxic T lymphocytes (Tc) function and proliferation. Glucocorticoids decrease chemotaxis of neutrophils and monocytes and the lysosomal enzyme release. They induce the transcription of gene for inhibition factor IFkB. As a result the transcription of genes for a variety of inflammatory and immune mediators is inhibited. They have little effect on humoral immunity.

High doses of methylprednisolone sodium succinate by IV route are used to reverse acute transplant rejection and acute exacerbations of some autoimmune diseases. Along with other immunosuppressants, glucocorticoids are used in case of bone marrow transplantation. Many autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus (SLE), psoriasis, systemic dermatomyositis and other skin diseases, bronchial asthma, inflammatory bowel and ocular diseases as well as exacerbations of multiple sclerosis.

2. Inhibitors of lymphocyte signalling to prevent immune cell activation and proliferation

**Calcineurin Inhibitors:** Cyclosporine, Tacrolimus.

**Cyclosporine:**

When a TH cell is activated, its cytoplasmic $Ca^{++}$-complexed with Calmodulin stimulates a phosphatase enzyme called calcineurin. This activated calcineurin phosphatase causes dephosphorylation of Nuclear Factor for Activated T cells (NFAT). Dephosphorylated NFAT enters into the nucleus to enhance IL-2 synthesis. Cyclosporine binds to a protein of TH cells. The resultant complex inhibits calcineurin activity and thus blocks activation of TH cells and production of IL-2 which is necessary for growth and differentiation of T cells. See Fig. 4.4.

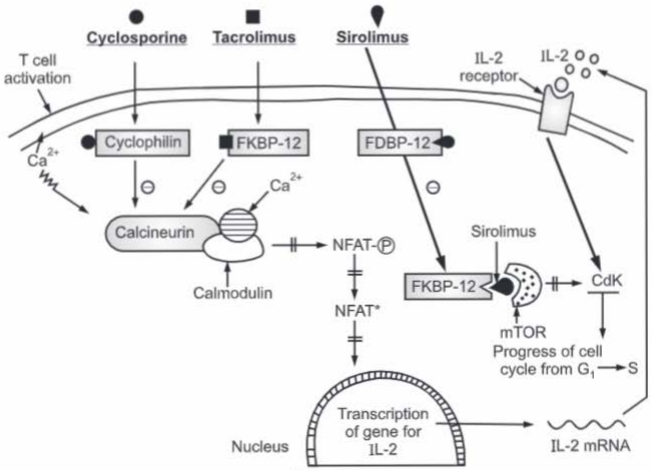



**Fig. 4.4**

Cyclosporine can be given either orally or intravenously. Its oral bioavailability is about 30%. Food decreases its absorption. It is metabolised by the enzyme CYP3A which can result in drug-drug interactions. Inactive metabolites are excreted in bile and then in faeces but minimal in urine. Plasma half-life is about 24 hours.

**Therapeutic Uses:**

It is used for following indications:

- To prevent graft rejection in solid organ transplant like heart, kidney and liver.
- To prevent/control certain autoimmune disorders like rheumatoid arthritis and psoriasis.
- To treat other T-cell mediated diseases like atopic dermatitis, endogenous uveitis, inflammatory bowel disease and nephritic syndrome.

**Adverse Reactions:**

It is nephrotoxic, neurotoxic and hepatotoxic. It can cause hypertension, hyperuricaemia and increase in LDL. It can also cause tremors, hirsutism and gingival hyperplasia. It may also cause intestinal fibrosis.

**Preparations:**

- Cyclosporine: 25 mg, 50 mg, 100 mg cap, 100 mg/ml injection: **Imusporin, Sandimmun neural.**

**Tacrolimus:**

It is much more potent than Cyclosporine but with similar mechanism of action. The only difference is that Tacrolimus binds to FK-binding protein (FKBP-12). It can be given orally or intravenously. It is metabolised by CYP3A to about 99%. Its plasma half-life is 7-8 hours. Its therapeutic uses are similar to that of Cyclosporine but it is more effective in liver transplant rejection. Topical Tacrolimus ointment is used for atopic dermatitis and psoriasis.

Its adverse reactions are similar to that of Cyclosporine except for the fact that hirsutism, hyperuricaemia and hyperlipidaemia are less but the risk of IDDM is more.

**Preparations:**

Tacrolimus: 0.5 mg, 1 mg, 5 mg cap: **Tacromus, Olmis, Pangraf;** 0.5 mg, 1 mg, 5 mg tab: **Crolin, Seegraf;** 0.03%, 0.1% ointment: **Tacrotor, Tacroderm**

**(3) Mammalian Target of Rapamycin (mTOR) Inhibitors:** Sirolimus, Everolimus

**Sirolimus:**

It is a macrocyclic lactone. It is also known as Rapamycin. Like Tacrolimus, Sirolimus binds to FKBP-12 to inhibit T lymphocyte activation and proliferation; but the complex does not block calcineurin. It inhibits the activation of mammalian target of Rapamycin (mTOR), which is a protein kinase enzyme having a key role in progression of cell cycle. As a result, T cells are arrested in $G_1$ phase.

Its oral bioavailability is 15%. Fatty meal decreases its bioavailability. Protein binding is 40-45%, mainly with albumin. It is extensively metabolised in liver by CYP3A4. Excretion is 91% in faeces and 2.5% in urine. Plasma half-life is 62 hours.

**Therapeutic Uses:**

It is used for following indications:

- To prevent acute rejection of organs like heart, kidney during organ transplant. It is used in combination with Cyclosporine and glucocorticoid.
- Sirolimus-eluted stents are available for use in coronary angioplasty. It inhibits local cell proliferation and reduces the risk of "in-stent" coronary restenosis.

**Adverse Reactions:**

It causes hyperlipidaemia, anaemia, thrombocytopenia and leukopenia. These defects are dose dependent and reversible. Nephrotoxicity is less than that of Cyclosporine and Tacrolimus. A combination of Tacrolimus + Sirolimus is more nephrotoxic. Delayed wound healing has been observed with Sirolimus.

**Preparations:**

- Sirolimus: 1 mg tab: **Rapacan.**

**Everolimus:**

It is a hydroxyethyl analogue of Sirolimus. The mechanism of action and drug interactions are similar to that of Sirolimus. Everolimus has a shorter half-life and needs lesser time to achieve steady state plasma concentration as compared to Sirolimus. mTOR inhibitors and calcineurin inhibitors enhance nephrotoxicity and chances of acute rejections.

**(4) Cytotoxic Agents to Reduce Lymphocyte Proliferation:**

Cytotoxic agents are further sub-classified as antimetabolites and alkylating agents. They are discussed below:

**Antimetabolites:** Azathioprine, Methotrexate, Mycophenolate mofetil, Leflunomide.

These drugs compete with essential components of cell metabolism.

**Azathioprine (AZA):**

It is a prodrug for 6-mercaptopurine (6-MP). The slow conversion of AZA to 6-MP and its final conversion to 6-thioGTP provides a product which is falsely incorporated into DNA of lymphocyte, making it non-functional. As a result, T cell activation and proliferation is prevented. AZA is used in organ transplant rejecton, rheumatoid arthritis and inflammatory bowel disease.

Its adverse reactions include bone marrow depression, leukopenia, thrombocytopenia, alopecia, increased risk of herpes complex and varicella infection, neoplasia, hepatotoxicity and GIT toxicity.

- Azathioprine: 50 mg tab: **Immuzat, Azoran, Immuran.**

**Methotrexate (MTX):**

MTX is a cytotoxic antimetabolite. It is used in cancer chemotherapy, has immunosuppressant action due to its action on lymphocytes and other cells of the immune system. It increases levels of adenosine. Adenosine has potent anti-inflammatory effects and also inhibits superoxide anion generation in neutrophils. It also enhances apoptosis of activated but not of resting CD4+ and CD8+ T cells. MTX is used to treat graft versus host disease, rheumatoid arthritis and psoriasis.

**Preparations**

- Methotrexate: 2.5 mg, 5 mg, 7.5 mg, 10 mg tab, 10mg/ml injection: **Oncotrex;** 2.5 mg, 5 mg, 7.5 mg, 10 mg tab, 15 mg/ml injection: **Imutrex, Folitrax**

**Mycophenolate Mofetil (MPM):**

Its active metabolite mycophenolic acid (MPA) inhibits proliferation and activation of T- and B- lymphocytes by inhibiting inosine monophosphate dehydrogenase type II (IMPDH-II) which is highly expressed on lymphocytes and is crucial for purine synthesis which is essential for DNA of T- and B- lymphocytes. MPM interferes with leukocyte adhesion to endothelial cells. IMPDH inhibition also decreases levels of guanosine, which regulates synthesis of inducible nitric oxide synthase (iNOS). Hence, decreased levels of nitric oxide (NO) also lead to decreased cytotoxicity by T cells and neutrophils.

**Therapeutic Uses:**

It is used for following indications:

- As a prophylactic for transplant rejection, both acute and chronic. It is generally used with glucocorticoids and calcineurin inhibitors.
- In rheumatoid arthritis, myasthenia gravis, autoimmune haemolytic anaemia and inflammatory bowel disease.

- Reducing replication of HIV virus which infects T lymphocytes and Epstein-Barr virus (EBV) which in turn infects B lymphocytes.

It is orally well absorbed. The metabolite micophenolic acid undergoes entero-hepatic circulation and is finally eliminated by kidney. Its adverse effects are exhibited on GIT, haemopoietic and liver.

**Preparations:**

- Mycophenolate Mofetil: 250 mg, 500 mg tab: **Mycofit, Mofetyl;** 250 mg, 500 mg cap: **Mycept.**

**Leflunomide:**

It is used in rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, Wegener's granulomatosis and polyoma virus nephropathy observed in immunosuppressed kidney transplant patients.

It inhibits T cell proliferation and production of auto-antibodies by B cells. It has a plasma half-life of 19 days. It undergoes entero-hepatic circulation. It is given in a loading dose of 100 mg orally, daily for 3 days initially. It is followed by 10-20 mg OD. Its adverse effects include diarrhoea, headache, nausea, rashes, mild alopecia and elevation in hepatic transaminases. It is contraindicated during pregnancy and lactation. Cholestyramine can be used to increase the clearance and reduce toxicity of Leflunomide.

**Preparations:**

- Leflunomide: 10 mg, 20 mg tab: **Lefra, Lefumide, Lisifen**

**(4) Alkylating Agents: Cyclophosphamide**

Cyclophosphamide is a unique immunosuppressant, since it suppresses B lymphocyte proliferation but can enhance T cell responses. As a result it is restricted to diseases of humoral immunity, particularly systemic lupus erythematosus. It is used for treating lymphoma, Hodgkin's disease, multiple myeloma and carcinoma of testes, lung, breast, prostate and ovary. Its adverse effects include myelosuppression, hepatotoxicity, alopecia, SIADH, stomatitis and nausea. It causes haemorrhagic cystitis due to generation of acrolein, a nephrotoxic metabolite. Mesna is usually co-administered with Cyclophosphamide to prevent haemorrhagic cystitis. Mesna conjugates with acrolein in urine, reducing the incidence of renal toxicity.

**(5) Cytokine Inhibitors (Anticytokine-Antibodies):**

TNF-α and IL-1 are pro-inflammatory cytokines implicated in pathogenesis of rheumatoid arthritis and Crohn's disease. IL-2 binds to activated T lymphocytes and promotes their proliferation. Hence, cytokine inhibitors are useful as immunosuppressants.

**(a) Tumour Necrosis Factor-α (TNF-α) inhibitors:** Activated cytotoxic TH-1 cells, macrophages and mast cells secrete TNF-α which binds to TNF receptors present on fibroblasts, neutrophils and vascular endothelial cells. In addition, there are soluble forms of TNF-α receptors in serum and synovial fluid. Activation of TNF-α results in release of cytokines viz IL-1, IL-6 and adhesion molecules which promote leukocyte aggrevation and migration.

Etanarcept, Infliximab and Adalimumab are discussed under monoclonal antibodies. (4.2.4)

**(b) Interleukin-1 (IL-1) receptor antagonists:** All activated mononuclear cells generate IL-1, which in turn enhances the production of IL-6, of adhesion molecules and release of metalloproteinase. IL-1 also stimulates cell proliferation. The role of metalloproteinase is to degrade the cellular matrix in preparation for their proliferation. The naturally occurring endogenous antagonists of IL-1 receptor is IL-1RA.

Anakinra is discussed under monoclonal antibodies. (4.2.4)

**(c) Interleukin-2 (IL-2) receptor antagonists:** IL-2 mediates early but crucial steps in T cell activation. CD25 is the high affinity IL-2 receptor expressed on activated T cells. Thus, anti-CD25 antibodies can specifically act on those T cells which have been activated by MHC-antigen complex stimulus. There are two monoclonal antibodies against IL-2α receptor. They are Daclizumab, Basiliximab. They are discussed under monoclonal antibodies.

**(6) Antibodies Against Specific Immune Cells Molecules:**

The acquired immune system on recognising the foreign antigens generates an immune response by way of activation and clonal expression of various immune cell molecules like CD2, CD3, CD8 etc. Treatment with exogenous antibodies targeted against several such molecules deplete the immune system of these reactive cells which participate in lymphocyte activation and proliferation. They are of two types: polyclonal and monoclonal antibodies.

**(a) Polyclonal antibodies:** Antithymocyte Globulin (ATG) is a highly purified solution of Y-globulins with antithymocyte activity. It is obtained by immunising horse's or sheep with human lymphocytes. It is available as freeze dried sterile powder for intravenous administration. ATGs, being polyclonal cytotoxic antibodies, target several epitopes such as CD2, CD3, CD8, CD11a, CD18, CD25, CD44 and MHC I and II molecules expressed on the cell surface of APCs or T cells. Administration of ATG results in depletion of T lymphocytes as a consequence of compliment-dependent lysis followed by opsonisation by macrophage-monocyte system. There is minimal effect on B lymphocytes or monocytes. Hence, humoral antibody formation remains relatively intact despite inactivation and depletion of T cells. This results in impairment of delayed hypersensitivity and cellular immunity.

ATG is used to prevent allograft rejection viz kidney transplant. The adverse effects include local pain and erythema at the site of injection. ATG which target T lymphocytes cause cytokine release syndrome which is caused due to initial activation of T cell and cytokine release. The symptoms include fever, chills, dyspnoea, nausea, vomiting, hypotension and rashes.

**Preparations:**

- **Antithymocyte globulin (ATG):** 25 mg/vial injection: **Thymoglobuline (rabit);** 50 mg/ml injection: **Atgam;** 100 mg/5 ml vial for injection: **Lymphoglobuline (equine)**

**(b) Monoclonal antibodies:** Alemtuzumab, Muromonab. These are discussed under monoclonal antibodies (4.6).

1. Inhibitors of immune cell adhesion and activation: Efalizumab, Alefacept. These are discussed under monoclonal antibodies (4.6).
2. Miscellaneous: Rho (D) immune globulins.

The name Rh system originates from Rhesus monkey. It is based on the type of antigen present on the surface of erythrocytes. People whose RBCs have Rh (D) antigen are designated as $Rh^+$ and those who lack it are designated as $Rh^-$. Normally plasma does not have anti-Rh antibody. If a $Rh^-$ person receives $Rh^+$ blood, the body starts to make anti-$Rh^+$ antibodies which then remain in circulation. If a second transfusion of $Rh^+$ blood is given later, then these antibodies react and can cause haemolysis of the donated blood with severe reactions.

Such Rh incompatibility may occur during pregnancy. Normally, there is no direct contact between the maternal and foetal blood during pregnancy. However, if a small amount of $Rh^+$ blood leaks from the foetus through placenta into the blood stream of $Rh^-$ mother (as during delivery or abortion), the mother will start making anti-$Rh^+$ antibodies. The new born baby would not be affected as it is not a second exposure. However in subsequent pregnancy, the mother's anti-$Rh^+$ antibody can cross placenta and enter into foetal circulation. If the foetus is $Rh^-$ then there is no problem. However, if the foetus is $Rh^+$, haemolysis of foetal blood can occur; which is called as Haemolytic Disease of Newborn (HDN) resulting in abortion.

HDN can be prevented by giving an injection of anti-Rh gamma globulin (RhoGAM) to $Rh^-$ mother soon after delivery or abortion. The usual dose of Rho (D) immune globulin is 2 ml intramuscularly. It contains about 300 mg of anti-RhoD-IgG.

**Preparations:**

- Rho (D) immune globulin: 300 mg/vial injection: **Winrhosd, Rhesumen, Rhogam**

## 4.5 PROTEIN DRUGS

Protein drugs belong to following categories:

- Enzymes and other proteins.
- Genetically recombinant proteins.
- Monoclonal antibodies (MAbs).
- Biosimilars.

Genetically modified proteins (recombinant cytokines under immunostimulants (Section 4.4.1), biosimilars (Section 4.7) and MAbs (Section 4.6) have been discussed elsewhere. Only enzymes and other proteins are discussed here.

### 4.5.1 Enzymes

Enzymes are protein substances which are highly potent. They need to be administered parenterally because they are inactivated in GIT. The only exception is of enzymes like pancreatin, diastase, pepsin and papain which are used for disorders of GIT. Because of their proteinic nature, they are likely to evoke allergic responses when given parenterally. Because of complicated method of preparation, they are relatively costlier. They are sub-classified as

digestant enzymes, thrombolytic/haemostatic enzymes, mucolytic enzyme and miscellaneous enzymes. They are discussed below.

**(1) Digestant Enzymes**

Digestant enzymes aid in digestion in the GIT.

**Pepsin:** It is a proteolytic enzyme, obtained from the glandular layer of the fresh stomach of the hog. It is administered orally in the dose of 0.5-1 gm. It is useful in gastric achylia, a condition characterised by defective acid and pepsin secretion by the stomach. Gastric achylia is observed in patients with carcinoma of the stomach and pernicious anaemia.

Another enzyme, papain, obtained from vegetable source (papaya), has also proteolytic properties.

**Rennin:** It is a partially purified milk curdling enzyme, obtained from the glandular layer of calf stomach. It is used just like pepsin. It is also used in preparation of cheese.

**Pancreatin:** It contains the enzymes amylase, trypsin and lipase and is obtained from pancreas of hog or ox. It is employed as a replacement therapy in chronic pancreatitis, obstruction caused by the cancer of head of pancreas, cystic fibrosis, and after total gastrectomy and pancreactomy. It is not useful in GI disorders unrelated to pancreatic enzyme insufficiency. It is administered orally in enteric coated capsules, to prevent its gastric inactivation. Large doses are needed because the enzymic activity is relatively less. Pancreatin should be used only as an adjunct to reduction in dietary fat intake. Prolonged use can cause fibrosing colonopathy.

**(2) Thrombolytic/Haemostatic Enzymes:**

**Hirudin:**

It is a potent antithrombin polypeptide obtained from the medical leech *Hirudo medicinalis*. Now it has been obtained by recombinant DNA technique, **Lepirudin**. It binds tightly to thrombin. It inactivates free as well as fibrin-bound thrombin. Its effect does not require antithrombin III or other cofactors. It not only prevents conversion of fibrinogen to fibrin, but also blocks thrombin-catalysed platelet aggregation and activation of other clotting factors. It inhibits disseminated intravascular coagulation and venous as well as arterial thrombosis more effectively. Its action is very short and has to be given by intravenous infusion. It has no antidote.

**Biviluridin** is an analogue of Hirudin, claimed to be relatively safer.

**Human antithrombin III concentrate:** It is prepared from pooled human plasma. It is heat treated in solution at $60^0$C for atleast 10 hours in order to inactivate the pathogenic viruses. It is used either alone or along with heparin to treat patients with a rare hereditary disorder, named antithrombin III deficiency which is associated with recurrent thrombotic episodes.

**Streptokinase and Streptodornase:** It is produced by certain strains of beta haemolytic streptococci. It causes fibrinolysis and dissolution of clot mainly by converting the intrinsic plasminogen present in the fibrin clot to its active form plasmin. In addition, it is also capable of activating the plasminogen in body fluids (extrinsic plasminogen) to plasmin; but this

mechanism is of secondary importance. It has maximum enzymatic activity between pH 7.3-7.6 of approximately 11-13 minutes. Its activity caeses shortly after therapy is discontinued.

It is used for following indications:

1. Myocardial infarction
2. Ischaemic stroke
3. Pulmonary embolism
4. Acute peripheral arterial occlusion
5. Deep vein thrombosis
6. Unstable angina

Its use in myocardial infarction is life saving. During this condition, it is given as an IV dose of 1.5 million units over 60 minutes. It is followed by 75-150 mg of Aspirin by mouth, daily for 4 weeks. For deep vein thrombosis, the dose of 2,50,000 uints are given intravenously in 30 minutes followed by 1,00,000 units every hour for 24-72 hours.

**Streptodornase** is not a single enzyme but a group of rapidly acting enzymes which promote the depolymerisation of the complex nucleoproteins derived from degenerated leukocytes and injured tissue cells. They act directly and not through plasminogen activation. Their action results in a rapid conversion of thick, viscous and purulent material to thin, easy flowing fluid. The enzymes do not act on nucleoproteins of living cells. Their optimum activity is observed between pH 7.0-8.5 and requires the presence of magnesium ions.

Both streptokinase and streptodornase are stable for several months in desiccated form but solutions at room temperature deteriorate rapidly.

Both of them cause adverse reactions like urticaria, rash, fever and anaphylaxis. A febrile reaction may occur. They should not be employed in presence of acute cellulitis and inflammation, since it may encourage spread of local infection. Since these substances are bacterial antigens, therapy may result in rapid antibody formation rendering further treatment ineffective. Haemorrhagic stroke is a possible complication of thrombolytic therapy.

**Alteplase (rtPA):** It is a recombinant tissue-type plasminogen activator, which is a natural protein in man. It preferentially activates plasminogen bound to fibrin clot and avoid systemic activation of plasminogen; thus leading to fibrinogen depletion and reduction of bleeding. It is preparaed by recombinant DNA technology. It is as effective as streptokinase but may be safer. It has a short half-life of 8 minutes in circulating plasma. It is metabolised by liver. It is given in the dose of 10 mg IV over 1-2 minutes, followed by IV infusion of 50 mg over 1 hour; then 40 mg over next 2 hours with total maximum dose of 100 mg over 3 hours. Heparin 5000 units is given as IV bolus prior to administration of Alteplase.

**Reteplase and Tenecteplase:** Reteplase and Tenecteplase are recombinant variants of human rt-PA. They have long plasma half-lives and can be given as bolus injection.

**Urokinase:** The enzyme was originally isolated from human urine. Now it is obtained from cultured human renal cells. It is a potent direct plasminogen activator. It is non-

antigenic, non-pyrogenic and does not cause allergic reactions. It lacks fibrin specificity and is expensive. Usually it is administered intravenously in an initial dose of 4400 units/Kg in 10 minutes followed by continuous infusion of the same dose per hour for 12-24 hours. Its use is followed by administration of heparin and that of oral anticoagulants. It is also used to lyse fibrin or blood deposits in the anterior chamber of the eye. For this purpose, 5000 units of the enzyme in 2 ml of sterile physiological saline at pH 7.2-7.6 are instilled into anterior chamber.

In the treatment of acute myocardial infarction, a new dosage has been used where coronary thrombolysis is initiated with a preactivation dose of urokinase in 500,000 units bolus in the pre-hospitalization phase, at home or in the mobile coronary care unit. It is followed by 7,50,000 units of streptokinase in the hospital.

Urokinase is contraindicated in conditions of hypofibrinogenaemia and hypocoagulability of blood.

**Anistreplase and Eminase:** These are examples of acylated plasminogen-streptokinase activator (APSAC) complex.

Properties of thrombolytic enzymes are presented in Table 4.2.

**Table 4.2 : Comparative properties of thrombolytic enzymes**

| Characteristic | Streptokinase | Anistereplase | Urokinase | Alteplase |
|---|---|---|---|---|
| Plasma half-life (minutes) | 15-25 | 50-90 | 15-20 | 4-8 |
| Fibrin specificity | Minimal | Minimal | Moderate | Moderate |
| Plasminogen binding | Indirect | Indirect | Direct | Direct |
| Potential for allergic reaction/hypotension | Yes | Yes | No | No |
| Typical dose | 1.5 million units | 30 units | 3 million units | 100 mg |
| Administration | Intravenous over 60 minutes | IV bolus in 2 minutes | 1.5 MU IV bolus, then 1.5 MU IV over 1 hour | 15 mg IV bolus; rest over 90 minutes |

MU means million units.

**Arvin:**

It is a purified enzyme obtained from the venom of the Malayan Pit Viper, *Agkistroden rhodostoma*. The enzyme has following properties:

- It converts fibrinogen to an imperfect fibrin polymer which breaks up easily in the circulation and is lysed.
- It produces fibrinogen depletion independent of the coagulation and fibrinolytic enzyme systems.

- It does not affect platelet function.
- The therapy is controlled by measuring plasma fibrinogen.

The enzyme has been used in the treatment of venous thrombosis. It is administered intravenously in the dose of 2-3 units/Kg over a period of 6-8 hours, followed by slow IV injection of 2 units/Kg every 12 hours. It promptly reduces fibrinogen levels, the peak anticoagulant activity occurring 8-12 hours after its administration. The lowered fibrinogen levels return to normal within 3 weeks after cessation of therapy. It can also be used intramuscularly or sub-cutaneously.

The advantage of enzyme is its mechanism of action. It does not cause haemorrhagic tendency. However, bleeding may occur from a silent peptic ulcer or a surgical wound. Haemolytic anaemia, urticaria and unilateral impairment of vision have been reported. Specific antivenom antidote is available to treat the toxicity. Resistance to the enzyme may occur, on intramuscular administration, due to antibody formation.

**(3) Mucolytic Enzyme:**

**Pancreatic dornase:** It is a deoxyribonuclease enzyme obtained from beef pancreas. It decreases viscosity of secretions by degrading deoxyribonucleoprotein. It acts extracellularly and does not attack living material. The preparation is claimed to be effective in changing thick, gelatinous sputum to thin milky material, when administered by aerosol.

The adverse reactions are mainly allergic due to sensitivity to beef protein.

**(4) Miscellaneous Enzymes:**

**Hyaluronidase:** This enzyme, prepared from mammalian testes, acts by depolymerising hyaluronic acid, an essential component of the intercellular ground substances which determines the permeability of the tissues. It is administered subcutaneously, increases the tissue permeability or exhibits spreading activity.

It is an odourless, fluffy powder containing not less than 300 units of activity per mg. It is employed to promote rapid absorption of drugs and fluids given subcutaneously or intramuscularly. It is particularly useful in aiding absorption of relatively large quantities of fluids, administered subcutaneously in infants and young children, in whom intravenous injection may be difficult. 1500 units of the enzyme are added to each litre of the fluid to be administered.

Sodium hyaluronate in highly purified form is used in a number of ophthalmic surgical procedures. It should not be applied directly to the cornea and should not be used to reduce the swelling of bites and stings.

It is antigenic and may produce allergic reactions occasionally. Because of the danger of spreading infection, the enzyme should not be injected into or around an infected area. Malignancy is also considered a contraindication for its administration.

**Trypsin:** This enzyme is obtained from an extract of the ox pancreas. It is available as a white powder soluble in water. The enzyme is active in pH range of 5-8 with an optimum activity at pH 7. It directly hydrolyses natural proteins including respiratory mucins. It does not require a cofactor for its effect.

It has therapeutic applications similar to streptokinase-streptodornase. For infiltration or by instillation, it is used as a solution containing 3-5 mg of the enzyme per ml. The dry powder may be applied every 15-30 minutes to small areas and every 3 hours to large areas; wet dressings and irrigations should be repeated every 3 hours. Small gelatine capsules containing the enzyme may be inserted into inirrigable sinuses and fistulae. An aerosol of trypsin has been used to liquefy excessive bronchial secretions.

Its adverse reactions are similar to those of streptokinase-streptodornase. Application of the dry powder to surface lesions may cause a severe burning sensation. Intramuscular injection may be followed by pain and induration at the site of injection and occasionally by fever, leukocytosis, angioneurotic oedema and urticaria. It should be used cautiously in presence of renal damage and should be avoided in individuals with hepatic insufficiency. **It should never be given intravenously.**

Proteolytic enzymes from *Carica papaya* (papase) and concentrated protease (bromelains) obtained from pineapple plant are used like trypsin. They act by depolymerising the soft fibrin deposits in the inflamed areas and by facilitating the drainage of fluids.

**Chymotrypsin:** It is a proteolytic enzyme obtained from the bovine pancreas. It is available as tablets containing 50,000 units of the enzyme per tablet. A mixture of trypsin and chymotrypsin is available as Chymoral. It is used as an adjunct to the conventional treatment of traumatically induced inflammation and oedema of soft tissues. It is applied locally or given orally.

**Alphachymotrypsin:** It is mainly used in ophthalmology for dissolving the suspensory ligament of the lens to facilitate the dissection of the lens during intra-capsular extraction of cataract. The procedure is called as zonulolysis. It is used as 0.2-0.5 ml of a freshly prepared 1:5000 solution injected slowly behind the lens into the posterior chamber. The adverse effects include transient glaucoma, wound disruption, loss of vitreous and rarely retinal damage, if it penetrates the vitreous. It can also be applied locally.

**Collagenase:** The enzyme is derived from fermentation of *Clostridium histolyticum*. It acts on both denatured and undenatured collagen. Newly formed collagen and healthy tissue collagen are not attacked. The activity is optimum at pH 6-8. It is used for debridement of dermal ulcers and in severe burns. It is applied in the form of an ointment once daily.

**Serratiopeptidase:** It is a proteolytic enzyme administered orally. It is claimed to be useful for digesting necrotic tissue, cell debris, cellular exudates and coagulated blood. It is promoted for oral treatment of inflammatory oedema and hematoma.

**L-asparaginase:** It deaminates asparagin to aspartic acid. it is prepared from *E coli*. Asparagin is a non-essential amino acid synthesised by mammalian tissue cells. Some malignant tumours are unable to synthesise asparagin and are dependent on supplies from the host. Asparaginase acts by depleting asparagin from the host, thus denying the malignant cells of an essential metabolite. It is relatively non-toxic to normal dividing cells in comparison to the neoplastic cells. It is given intravenously and provides relief in cases of lymphoblastic leukaemia and reticulum cell sarcoma. It may cause pyrogenic reactions and sensitization.

### 4.5.2 Other Proteins

**Fibrinogen:** It is a sterile fraction form human plasma. It is used for restoring normal fibrinogen levels in haemorrhagic complications caused by acute afibrinogenemia. Fibrinogen and thrombin may be employed together for local haemostasis.

**Antihaemophilic globulin (AHG):** Haemophilia A and Christmas disease (Haemophilia B) are the two most common hereditary haemorrhagic states due to deficiency of specific clotting factors VIII and IX respectively. AHG or concentrate of factor VIII is highly effective in the treatment of classical haemophilia A. High potency human AHG is prepared from pooled, normal, human plasma. Now it is prepared by recombinant DNA technique. It is given in a dose of 15-60 units/Kg daily. Simultaneously use of fibrinolytic inhibitors like EACA can reduce the dose of required AHG. In case of non-availability of AHG, fresh plasma or blood transfusion is used. The half-life of injected factor VIII in a haemophilic is about 12 hours. Desmopressin, which causes release of AHG from its stores, transiently increases its blood level and is helpful in the treatment of mild-moderate haemophilic bleeding.

Pure recombinant factor VIII, factor IX and activated factor VII are also available. In patients with Christmas disease, fresh or stored plasma infusion is indicated to replenish factor IX.

## 4.6 MONOCLONAL ANTIBODIES: TARGET DRUGS TO ANTIGEN

Monoclonal antibodies, target drugs to antigen

MAbs are single species of antibody which recognise and react with a specific antigen only. They are produced by cloning of hybrid cells created by fusing an immortal cell from mouse myeloma with a B-cell producing antibody against a desired antigen. The resulting hybridomas have an ability of B-lymphocytes to secrete a single species of antibody and the capability of cancer cells to proliferate endlessly. They exert cytotoxic action and facilitate apoptosis.

Murine MAbs, generated from rodents like mouse are usually not preferred since they have a shorter half- life and induce a human antimouse-antibody allergic response. Hence a chimerised MAbs are commonly used; the word chimerised indicates partly human and partly mouse MAbs. The names of chimeric MAbs usually end up with "ximab" (eg Rituximab) while those of humanised MAbs end up with "Umab" (eg Trastuzumab).

Monoclonal antibodies (MAbs) belong to different types: anticytokine MAbs, IL-2 receptor antagonists, MAbs against specific immune cell molecules, inhibitors of immune cell adhesion and activation and for treating cancer.

**Anticytokine MAbs:** Etanercept, Infliximab, Adalimumab, Anakinra

**Etanercept** has limited use because of following reasons:

- It does not discriminate between TNF-α and TNF-β. Binding to TNF-β promotes IL-2 mediated T cell proliferation.
- It has a long half-life of 115 hours and needs few weeks to achieve steady state plasma level.
- On discontinuation, symptoms of arthritis appear within a month.

**Infliximab** is a chimeric (25% mouse and 75% human) monoclonal antibody. It crosslinks with membrane bound TNF-α receptors on cell surface to inhibit T cell and macrophage function and to prevent release of other pro-inflammatory cytokines like IL-1, 6, 8 along with collagenase and metalloproteinases. It has a longer half-life of 200 hours and onset time of 3 weeks; however it does not bind to TNF-β. It is used in Crohn's disease and rheumatoid arthritis. Better clinical benefits are obtained with Methotrexate.

**Adalimumab** is a human recombinant monoclonal antibody to TNF-α. It does not bind to TNF-β. It is less antigenic than Infliximab. Its serum half-life is of 2 weeks. It is used for rheumatoid arthritis. It is administered as a single dose of 40 mg/0.8 ml sub-cutaneously every 14 days.

**Anakinra** is a recombinant form of IL-1RA which inhibits interaction of IL-1 with immune cells. It is used for the treatment of rheumatoid arthritis. It is given sub-cutaneously in a dose of 100-150 mg daily. Pain at the site of injection is the most common adverse effect. Flu like symptoms with headache may also occur.

**IL-2 receptor antagonists:** Daclizumab, Basiliximab.

IL-2 mediates early but crucial steps in T cell activation. CD25 is the high affinity IL-2 receptor expressed on activated T cells. Thus anti-CD25 antibodies can specifically act on those T cells which have been activated by MHC-antigen complex stimulus. Two such MAbs are discussed below:

**Daclizumab** is a chimeric monoclonal antibody produced by fusion of murine anti-CD25 antibodies with human $IgG_1$.

**Basiliximab** is a murine:human (10% murine and 90% human) chimeric monoclonal anti-CD25 antibody produced by recombinant DNA technology.

Both Daclizumab and Basiliximab block the α-chain of IL-2 receptor located on the surface of activated T cells. They are used for the prophylaxis of acute organ transplant rejection. Daclizumab has lower affinity to CD25 as compared to Basiliximab. Both drugs can be used in combination with glucocoriticoids, Cyclosporine or Azathioprine.

**MAbs against specific immune cell molecules:** Omalizumab, Muromonab-CD3, Alemtuzumab.

**Omalizumab** is a recombinant humanised MAb used for treating allergic asthma which is resistant to inhaled glucocorticoid therapy. It inhibits the binding of IgE to the Fc receptor on basophils and mast cells which suppresses IgE mediated release of mediators like histamine and leukotrines.

It neutralises free IgE in circulation by forming a high affinity anti-IgE complex.

**Muromonab-CD3 (anti-CD3 or OKT3)** is a murine MAb against human CD3, which is a signalling molecule for activation of T cell receptor (TCR). CD3 is expressed both on CD4+ and CD8+ T cells. Hence treatment with Muromonab depletes the total circulating T cells from the blood, which leads to activation of complement. It is used for prevention of acute allograft rejection after kidney, liver and heart transplant. Adverse effects include "cytokine release syndrome" which can be minimised by using glucocorticoids with anti-histamine.

**Alemtuzumab (anti-CD52 MAb or Campath-1H)** is a glycoprotein expressed on normal and malignant T- and B- lymphocytes, monocytes, NK cells and macrophages. Alemtuzumab is a humanised anti-CD52 MAb which binds to CD52 and causes prolonged lymphopenia. It is recommended to treat B cell chronic lymphocytic leukaemia where prolonged and sustained suppression of lymphocytes is desirable. It induces cell death through antibody dependent cellular cytotoxicity, compliment-dependent cytotoxicity and apoptosis. Its adverse effects include infusion related toxicity, lymphopenia, neutropenia, thrombocytopenia and anaemia, which increases risk for opportunistic infections.

**Inhibitors of immune cell adhesion and activation:** Efalizumab, Alefacept

**Efalizumab** is a humanised $IgG_1$ MAb which targets CD11, a chain of LFA-1 and blocks its activity. It is used for treatment of psoriasis. It reduces incidence of acute kidney transplant rejection. Its efficacy is increased when used with glucocorticoids, Cyclosporine and MPM.

**Alefacept** is an engineered human LFA-3 + $IgG_1$ fusion protein. The LFA3 moiety binds to CD2 present on T lymphocytes blocking the interaction between LFA3 present on dendritic cells and CD2 present on T cells. It prevents T cell activation. It is used to treat psoriasis.

**Abciximab** is a monoclonal antibody which causes platelet receptor blockade and inhibits platelet aggregation. It is given intravenously. The maximum effect is seen after 2 hours and lasts for 10-12 hours. Small amount of the drug can be detected on circulating platelets for 7-14 days. It is an effective antithrombic agent in acute myocardial ischaemic syndrome which requires precutaneous coronary intervention. It acts synergistically with Aspirin. The beneficial effect lasts for about 6 months. The major adverse reaction is bleeding. The use of antiplatelet drugs may unmask an underlying defect in haemostasis.

**Anticancer MAbs:** Rituximab, Epratuzumab, Alemtuzumab, Tratsuzumab, Cetuximab, Panitumumab, Bevacizumab and Edrecolomab

Clinical uses of each of them are indicated below:

**Rituximab** is a chimeric MAb used for treating B cell lymphoma and chronic lymphocytic leukaemia.

**Epratuzumab** is a humanised MAb used for treating non-Hodgkin's lymphoma and SLE.

**Alemtuzumab** is a humanised MAb used for treating B cell chronic lymphoid leukaemia and T cell lymphoma.

**Trastuzumab** is a humanised MAb used for treating breast cancer.

**Cetuximab** is a chimeric MAb used for treating colorectal cancer, non-small cell lung carcinoma, breast and pancreatic carcinoma.

**Panitumumab** is a humanised MAb used for treating colorectal cancer.

**Bevacizumab** is a humanised MAb used for treating metastatic colorectal cancer, renal cell carcinoma and breast cancer.

**Edrecolomab** is a murine MAb used for treating colorectal cancer.

**Preparations:**

Some of the currently available antibodies are listed in table 4.3.

**Table 4.3: Some of the currently available MAbs**

| Sr. No. | Generic name | Trade name | Indications |
|---|---|---|---|
| 1. | Muromonab | **Orthodone, OKT 3** | Renal graft rejection |
| 2. | Basiliximab | **Simalect** | Renal graft rejection |
| 3. | Daclizumab | **Zenepax** | Renal graft rejection |
| 4. | Infliximab | **Remicade** | Rheumatoid arthritis, Crohn's disease |
| 5. | Trastuzumab | - | Breast cancer |
| 6. | Rituximab | **Herceptin** | Metastatic breast cancer |
| 7. | Abciximab | **Reopro** | Antiplatelet |
| 8. | Palivizumab | **Synagis** | Antiviral |
| 9. | Gemtuzumab | - | Acute myeloid leukaemia |

## 4.7 BIOSIMILARS

A biosimilars is a biologic medical product that is almost an identical copy of an original product that is manufactured by an innovator company. Biosimilars are officially approved versions of original innovator products and can be manufactured when patent for the original product expires. Recombinant drugs like insulin, human growth hormone, interferons, erythropoietin, monoclonal antibodies are examples of biosimilars.

Reference to the innovator product is an integral component of the approval.

Unlike with generic drugs of small molecules (molecular weight < 1000), biologics generally exhibit high molecular complexity and may be quite sensitive to changes in manufacturing processes. Bigger the molecule, greater are the number of atoms that make up its structure and greater is the complexity. Thus biologics are more complex, consisting of primary (amino acid sequence) and secondary (α-helix and β-pleated sheet) structures, which are folded into complicated 3D tertiary structures. In some biopharmaceuticals, stable associations of tertiary structures of individual proteins form a quaternary structure. After synthesis, these structures are further modified by post-translational modifications like glycosylation or sialylation, which may be crucial for biological activity. Further due to larger size and structural complexity, characterisation of a biosimilars presents an enormous challenge.

Difference between small molecule drugs and biologic drugs/biosimilars are presented in Table 4.4 and 4.5.

**Table 4.4: Product- related differences between small molecules and biologic drugs/biosimilars.**

| Sr. No. | Small-molecule drugs | Biologic drugs |
|---|---|---|
| 1. | Produced by chemical synthesis | Biotechnologically produced by host cell lines |
| 2. | Low molecular weight | High molecular weight |
| 3. | Well-defined physicochemical properties | Complex physicochemical properties |
| 4. | Stable | Sensitive to heat and shear (aggregation) |
| 5. | Single entity, high chemical purity, purity standards well established | Heterogenous mixture, broad specifications may change during development, difficult to standardise |
| 6. | Administered through different routes of administration | Usually administered parenterally |
| 7. | Rapidly enters systemic circulation through blood capillary | Large molecule primarily reach circulation via lymphatic system, subject to proteolysis during interstitial and lymphatic transit |
| 8. | Distribution to any combination of organ/tissue | Distribution usually limited to plasma and/or extracellular fluid |
| 9. | Often specific toxicity | Mostly receptor mediated toxicity |
| 10. | Often non-antigenic | Usually antigenic |

**Table 4.5: Manufacturing differences between small molecule drugs and biologic drugs/biosimilars.**

| Sr. No. | Small molecule drugs | Biologic drugs |
|---|---|---|
| 1. | Completely characterised by analytical methods | Difficult to characterise |
| 2. | Easy to purify | Lengthy and complex purification process |
| 3. | Contamination can be generally avoided; it is easily detectable and removable | High possibility of contamination, detection is harder and removal is often impossible |
| 4. | Not affected by slight changes in production process and environment | Highly susceptible to slight changes in production process and environment |

In case of synthetic drugs, once the patent life is over, a generic product is introduced by companies other than innovators. Similar thing can happen in case of biosimilars also. However, a biosimilars product may not be exactly replicating to that of innovator. A comparison between a biologic product, its biosimilars product and a generic version of a synthetic drug is presented in Table 4.6.

**Table 4.6: Comparison between biologic, biosimilars and a generic (of synthetic drugs)**

| Process | Biologic | Biosimilars | Generic |
|---|---|---|---|
| Manufacturing | Produced by biological process in first cell lines; sensitive to production process changes-expensive and specialised production; reproducibility difficult to establish | Produced by biological process in host cell lines; sensitive to production process changes-expensive and specialised production; reproducibility difficult to establish | Produced by using chemical synthesis; less sensitive to production process changes; reproducibility easy to establish |
| Clinical development | Extensive clinical study including phase I-III; pharmacovigilance and periodic safety updates needed | Extensive clinical study including phase I-III; pharmacovigilance and periodic safety updates needed | Often only phase I studies; short time line for approval |
| Regulation | Needs to demonstrate comparability; regulatory pathway defined by EMEA; currently no automatic substitution intended | Needs to demonstrate similarity; regulatory pathway defined by EMEA; no automatic substitution allowed | Needs to show bioequivalence; abbreviated registration procedures in Europe and USA; automatic substitution allowed |

EMEA: European Medicines Agency

Typical steps in manufacturing of a biological product are presented in figure 4.5.

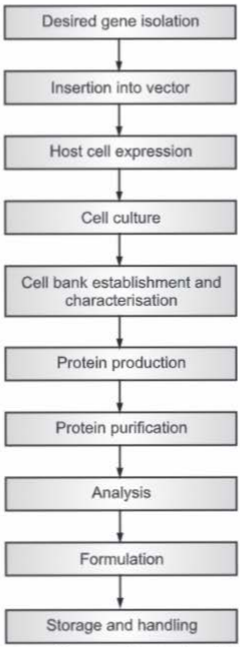



**Fig. 4.5: Typical steps in manufacturing biological product**

There are various steps in development of biosimilars`. It starts with physicochemical characterisation followed by biological characterisation, pre-clinical studies, clinical studies and pharmacovigilance. The process is presented in Fig. 4.6.

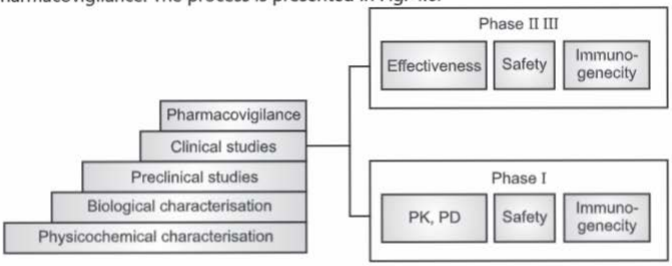



**Fig. 4.6: Stepwise development approach for a biosimilar**

Biosimilarity of a product is established by a stepwise approach including structure, function, animal toxicity, pharmacokinetics (PK) and pharmacodynamics (PD), immunogenicity and clinical safety as well as efficacy. The stepwise approach is presented in table 4.7.

**Table 4.7: Stepwise approach to demonstrate biosimilarity**

| Step | Role | Element |
|---|---|---|
| Structure | Serves as the foundation for biosimilars development. | Determine quality attributes in terms of amino acid sequence, higher- order structures, post translational modifications, eg glycosylation; analyse lot-to-lot variability. |
| Function | Serves as the foundation for biosimilars development. | Determine quality attributes in terms of pharmacological activity through in vitro or in vivo experiments; determine specific assays based on mechanism of action. |
| Animal toxicity | Useful when unresolved questions exist about the safety of a biosimilars based on studies of structure and function. | Comparative animal toxicity design depends on the unresolved questions identified through comparibility studies of structure and function. |
| PK and PD | Fundamental for demonstrating biosimilarity. | Assess bioequivalence in a sensitive population (PK); use a sensitive PD end point which is predictive of clinical outcomes, use crossover and parallel designs. |
| Immunogenicity | Evaluation of potential differences in incidence and severity of immune responses. | End points include antibody formation (binding, neutralising), cytokine levels etc; comparative parallel study can be used; analysis is done mainly within PK and PD and the efficacy and safety studies. |
| Clinical safety and efficacy | Required to answer unresolved questions based on PK and PD studies to demonstrate optimum biological activity. | Non-inferiority and equivalence study designs are used; specific clinical trialconducted; specific end point and population depends on FDA; FDA may be allowed to extrapolate to other FDA approved indications. |

Despite their heterogenecity, biosimilars must maintain consistent quality and clinical performance throughout their life cycle.

Regulatory bodies have their own guidance on requirements for demonstration of similar nature of two biological products in terms of safety and efficacy.

Cloning of human genetic material and development of in vitro biological production systems has allowed the production of any recombinant DNA-based biological substance for eventual development of drug. Monoclonal antibody technology combined with recombinant technology has made it possible to develop tailor made and targeted medicines. Gene based and cell based therapies are emerging as new approaches.

Recombinant therapeutic proteins are of a complex nature. They are composed of a long chain of amino acids, modified amino acids, derivatised by sugar moieties and folded by complex mechanisms. These proteins are made in living cells like bacteria, yeast, animal or human cell lines. The characteristics of a drug containing a recombinant therapeutic protein are determined by the process through which they are produced: choice of the cell type, development of the genetically modified cell for production, production process, purification process and formulation of the therapeutic protein into a drug.

Every biological product displays a certain degree of variability, even between different batches of the same product, which is due to inherent variability of the biological expression system and the manufacturing process. Any kind of reference product undergoes numerous changes in its manufacturing process. These range from change in the supplier of cell culture media to new purification methods or new manufacturing sites. It is mandatory for biosimilars to take both non-clinical and clinical tests which the most sensitive clinical models are asked to show to enable detection of differences between the two products in terms of human pharmacokinetics (PK) and pharmacodynamics (PD), efficacy, safety and immunogenicity. In addition, introduction of biosimilars also requires a specifically designed pharmacovigilance plan.

Pharmaceutical companies like Teva, Mylan, Sandoz have focussed on biosimilars. Indian companies like Sun Pharma, Aurobindo Pharma and Dr Reddy's Laboratories as well as Canada-based Apotex have shifted their focus to biosimilars.

Since biosimilars are newly evolving products, the regulatory environment is also evolving. In Europe, European Medicines Agency (EMA) has been a global leader for providing regulatory guidelines. In USA, FDA is providing regulatory guidelines next to EMA. The Biologics Price Competition and Innovation Act (BPCIA) of 2009 provides framework for biosimilars. World Health Organisation has published guidelines for evaluation of similar biotherapeutic products in 2009. In India, the manufacturer has to receive approval from multiple Government agencies like National Biotechnology Regulatory Authority (NBRA), Central Drug Standardisation Control Organisation (CDSCO) etc. A list of Indian companies, their partnership and related comments are presented in Table 4.8.

**Table 4.8: Capability of Indian Pharmaceutical Companies and their partnership for biosimilars.**

| Name of Indian Company | Partnership | Comments |
|---|---|---|
| Biocon | Mylan, Pfizer | Capabilities driven by strategic alliances with global leaders |
| Intas | Apotex | First Indian company to receive EU-GMP certification |
| Dr Reddy's | GSK | Partnership with GSK for assistance in manufacturing and marketing; have WHO certified cGMP manufacturing facility |
| Reliance (life sciences) | Reliance Genemedix | Have multiple cGMP facilities in India in addition to main plant in Ireland |
| Bharat Biotech | ThromboGenics | Partnership with ThromboGenix for product development. Evaluating for marketing partners in Europe |
| Lupin Pharmaceuticals | Lilly | Five manufacturing facilities across India; emerging capabilities in biosimilars |
| Cipla | BioMAbEGFR | 40% stake in MAb farm and 25% stake in BioMAbs in China to grow MAb capabilities |
| Shantha Biotechnics | International Vaccine Institute (IVI) | Subsidiary Shanthawest in US has developed 4 MAbs; R&D partnership with IVI |
| Wockhardt | – | Opened a Biotech park, designed according to USA and EMEA standards |

Some of the biosimilars products in Indian market are listed in Table 4.9.

**Table 4.9: Biosimilar products in Indian market**

| Company name | Biosimilars | Product description |
|---|---|---|
| Torrent Pharmaceuticals limited | Adfrar | Biosimilars Adalimumab for treatment of autoimmune disorders |
| | Toritz RA | Biosimilars Rituximab |

*... (Contd.)*

| Company name | Biosimilars | Product description |
|---|---|---|
| Dr Reddy's Lab | Reditux | Biosimilars Rituximab (targeting CD20) |
| | Grafeel | Filgrastim (recombinant granulocyte-macrophage colony-stimulating factor) |
| | Cresp | Darbepoetin α (recombinant erythropoietin) |
| | Peg-grafeel | Pegfilgrastim |
| Roche with Cipla | Actorise | Darbepoetin α |
| Intas Biopharm Ltd | Neukine | Filgrastim (recombinant G-CSF) |
| | Neupeg | PEGylated G-CSF |
| | Intalfa | Recombinant human interferon α2b |
| | Epofit | Recombinant erythropoietin |
| | Mbtas | Rituximab |
| Shantha Biotech/Merieux Alliance | Shanferon | Recombinant interferon α2b |
| | Shankinase | Recombinant streptokinase |
| | Shanpoietin | Recombinant erythropoietin |
| Reliance Life Sciences | ReliPoietin | Recombinant erythropoietin |
| | ReliGrast | Recombinant G-CSF |
| | ReliFeron | Recombinant interferon α2b |
| | Relibeta | Interferon β-la |
| | MIRel | Recombinant reteplase (tissue-Plasminogen Activator) |
| Wockhardt | Wepox | Recombinant erythropoietin |
| | Wosulin | Recombinant insulin |
| Biocon | Eripro | Recombinant human erythropoietin |
| | Biomab | Nimotuzumab (humanised mAB targeting epidermal growth factor) |
| | Nufil | Filgrastim, recombinant G-CSF |
| | Myokinase | Recombinant streptokinase |
| | Insugen | Recombinant human insulin |
| | Alzumab | Itolizumab |
| | Basalog | Insulin glargine |

## SUMMARY

**Urinary Tract Infections**

- Sulphonamides
- Tetracyclines
- Nitrofurantoin
- Mandelamine
- Nalidixic acid
- Cotrimoxazole
- Penicillins : Ampicillin, Carbenicillin, Piperacillin
- Aminoglycosides
- Cephalosporins
- Fluroquinolines
- Fosfomycin

**Sexually Transmitted Diseases (STDs)**

- Syphilis
- Gonorrhea
- Non-Gonococcal Urethritis (NGU)
- Chancroid
- Lymphogranuloma venereum
- Granuloma Inguinale
- Veneral warts
- Vaginitis

**Chemotherapy of Malignancy**

- Alkylating agents
- Antimetabolites
- Antibiotics
- Natural products
- Miscellaneous agents
- Protein Tyrosine Kinase Inhibitors
- Epidermal Growth Factor Receptor Inhibitors
- Proteosome Inhibitors
- Hormones and antagonists
- Monoclonal antibodies
- Histone Deactylase Inhibitors
- Protectants

**Immunopharmacology**

- BCG
- Levamisole
- Thalidomide
- Lenalidomide
- Recombinant cytokines : Aldesleukin
- Other recombinant interleukins
- Colony-stimulating factors
- Recombinant interferous

**Immunosuppressants**

- Glucocorticoids
- Calcineurin inhibitors : cyclosporine, Tacrolimus
- Mammalian target of Rapamycin inhibitors: Sirolimus, Everolimus
- Antimetabolites: Azathioprine, Methotrexate, Mycophenolate mofetil, Leflunomide
- Alkylating agents
- Cytokine inhibitors
- Antibodies: Polycolonal, Monclonal

**Protein Drugs**

**Enzymes**

- Digestant: Pepsin, Renin, Pancreatin
- Thrombolytic Haemostatic: Hirudin, Antithrombin III concentrate, Streptokinase, Streptodornase, Alteplase, Reteplase, Tenecteplase, Anistreplase, Eminase, Arvin
- Mucolytic Pancreatic dornase
- Miscellaneous: Hyaluronidase, Trypsin, Chymotrypsin, Alphachymotrypsin, Collagenase, Serratiopeptidase, L-asparginase

**Other Proteins**

- Fibrinogen
- Antihaemophilic globulin

**Monoclonal Antibodies**

- Anticytokine MAbs: Etanercept, Infliximab, Adalimumab, Anakinra
- IL-2 receptor antagonists: Daclizumab, Basiliximab
- MAbs against specific immune cell molecules: Omalizumab, Muromonab-$CD_3$, Alemtuzumab
- Inhibitors of immune cell adhesion and activation Efalizumab, Abciximab
- Anticancer MAbs: Rituximab, Epratuzumab, Cetuximab, Alemtuzumab, Tratsuzumab, Panitumumab, Bevacizumab, Edrecolomab

**Biosimilars**

- Adalimumab
- Rituximab
- Filgrastrim
- Darbepoetin $\alpha$ (erythropoietin)
- Peg filgrastim
- PEGylated G-CSF
- Interferon
- Streptokinase
- Reteplase
- Insulin
- Insulin glargine
- mAB targeting EGF

## REVIEW QUESTIONS

**Long Answer Questions**

1. Differentiate between acute and chronic UTI.
2. Classify drugs acting on UTI and discuss two drugs in each category.

3. Describe pathogenesis and treatment of syphilis.
4. Discuss pathogencity and treatment of gonorrhoea.
5. Discuss chemotherapy of malignancy.
6. Describe different phases of cell cycle.
7. Classify anticancer drugs with suitable examples.
8. What are adverse reactions related to anticancer drugs?
9. Comment on combination therapy for treatment of cancer.
10. What are immunostimulants? Describe any two.
11. What are recombinant cytokines used as immunostimulants?
12. Classify immunosuppressants with one example each.
13. Describe monoclonal antibodies along with their clinical uses.
14. What is clinical importance of Rho (D) immune globulins?
15. Classify enzymes along with their clinical uses citing suitable examples.
16. Describe biosimilars and compare them with small molecule drugs.
17. Compare and contrast biologics, biosimilars and generics.
18. What is stepwise approach to demonstrate biosimilarity?

**Short Answer Questions**

1. Comment on pathogenesis and bacteriology of UTI.
2. Write short notes on

| | | | |
|---|---|---|---|
| (i) | Nitrofurantoin | (ii) | Mandelamine |
| (iii) | Phosphomycin | (iv) | Nalidixic acid |
| (v) | Cotrimoxazole in UTI | (vi) | Non-gonococcal urethritis (NGU) |
| (vii) | Chancroid | (viii) | Lymphogranuloma venereum |
| (ix) | Granuloma enguinale | (x) | Veneral warts |
| (xi) | Vaginitis | (xii) | 6-mercaptopurine |
| (xiii) | 5-fluorouracil | (xiv) | Recombinant interferons |
| (xv) | Cyclosporine | (xvi) | Tacrolimus |
| (xvii) | Sirolimus | (xviii) | Everolimus |
| (xix) | Azathioprine | (xx) | Methotrexate |
| (xxi) | Mycophenolate Mofetil | (xxii) | Leflunomide |
| (xxiii) | TNF-α inhibitors | (xxiv) | IL-1 receptor antagonists |
| (xxv) | Arvin | (xxvi) | Mucolytic enzyme |
| (xxvii) | Hyaluronidase | (xxviii) | Trypsin |
| (xxix) | Collagenase | (xxx) | Serratiopeptidase |
| (xxxi) | Fibrinogen | (xxxii) | Antihaemophilic globulin |

3. What are STDs?
4. What is Jerish-Herxheimer reaction?
5. What are causes of cancer?
6. What are the growth factors related to cancer?
7. What are cell cycle transducers?
8. What is apoptosis?
9. Enlist MAbs for cancer.
10. Compare thrombolytic enzymes.

*Unit* ...**5**

# PRINCIPLES OF TOXICOLOGY AND CHRONOPHARMACOLOGY

Upon completion of this unit, the student should be able to:

- Understand principles of toxicology
- Understand about acute, sub-acute and chronic toxicity
- Understand about genotoxicity, carcinogenicity, teratogenecity and mutagenicity
- Understand principles of treatment of poisoning
- Understand clinical symptoms and management of selected drugs
- Understand about chronopharmacology

## 5.1 PRINCIPLES OF TOXICOLOGY

Toxicology is defined as that branch of science which deals with poisons. A poison is defined as any substance that causes a harmful effect when administered, either by accident or design, to a living organism. The study of toxicology serves society not only to protect humans and the environment from the deleterious effects of toxicants but also to facilitate the development of more selective toxicants such as anticancer and other clinical drugs and pesticides.

The measurement of toxicity is a complex issue. Toxicity may be acute or chronic, and may vary from one organ to another as well as with age, genetics, gender, diet, physiological condition or the health status of the organism. Exposure of humans and other organisms to toxicants may result from many activities: intentional ingestion, occupational exposure, environmental exposure, as well as accidental and intentional (suicidal or homicidal) poisoning. The toxicity of a particular compound may vary with the portal of entry into the body, whether through the alimentary canal, the lungs, or the skin. Following exposure there are multiple possible routes of metabolism, both detoxifying and activating, and multiple toxic end points as shown in Fig. 5.1.

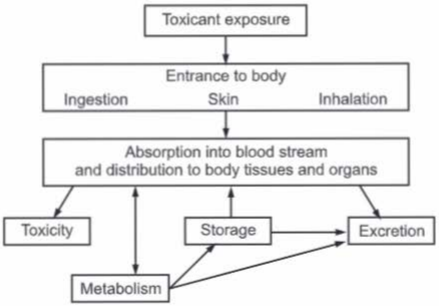



**Fig. 5.1**

Following principles should be considered while studying toxicology:

## 5.1.1 Modes of Toxic Action

It includes all events leading to toxicity in-vivo: uptake, distribution, metabolism, mode of action and excretion.

1. **Biochemical and molecular toxicology:** It involves events at biochemical and molecular level including enzymes, their action, generation of reactive intermediates/metabolites, interaction with macromolecules, gene expression and signalling pathways.
2. **Behavioural toxicology:** It deals with the effects of toxicants on animal and human behaviour.
3. **Nutritional toxicology:** It deals with the effects of diet on the expression of toxicity and with the mechanisms of these effects.
4. **Carcinogenesis:** It involves causing of cancer.
5. **Teratogenesis:** It involves deleterious effects on the foetus.
6. **Mutagenesis:** It involves toxic effects on the genetic material and their inheritance.
7. **Organ toxicity:** It involves adverse effect on organ functions e.g. neurotoxicity, hepatotoxicity, nephrotoxicity.

## 5.1.2 Measurement of Toxicants and Toxicity

It involves following questions: is the substance likely to be toxic? What is its chemical identity? How much of it is present? How can we assay its toxic effect?

1. **Analytical toxicology:** It is a branch of analytical chemistry concerned with identification and assay of toxic chemicals and their metabolites in biological materials.
2. **Toxicity testing:** It involves the use of living systems to estimate toxic effects.

3. **Toxicologic pathology:** It is a branch of pathology which deals with the effects of toxic agents manifested as changes in sub-cellular, cellular, tissue, or organ morphology.
4. **Structure activity studies:** It involves relationship between the chemical and physical properties of a chemical and the use of such relationships as predictors of toxicity.
5. **Epidemiology:** It deals with the relationship between chemical exposure and human disease in actual populations rather than in experimental setting.

### 5.1.3 Applied Toxicology

It includes various aspects of toxicology as they apply in the field or the development of new methodology or new selective toxicants for early application in the field setting.

1. **Clinical toxicology:** It is the diagnosis and treatment of human poisoning.
2. **Veterinary toxicology:** It is the diagnosis and treatment of poisoning in animals. It also involves transmission of toxins to the human population in meat, fish, milk and other food stuffs.
3. **Forensic toxicology:** It is concerned with medicolegal aspects, including detection of poisons in clinical and other samples.
4. **Environment toxicology:** It is concerned with the movement of toxicants and their metabolites/degradation products in the environment and in food chains and with the effect of such contaminants on individuals and populations.
5. **Industrial toxicology:** It is a specific area of environmental toxicology which deals with work environment and constitutes industrial hygiene.

### 5.1.4 Chemical Use Classes

It includes toxicology aspects of the development of new chemicals for commercial use. It also involves many natural products which are isolated and used for commercial purpose.

1. **Agricultural chemicals:** It includes insecticides, herbicides, fungicides and rodenticides.
2. **Clinical drugs:** It involves toxicity of drugs used in clinical practice.
3. **Drugs of abuse:** It involves chemicals taken for psychological or other effects and may cause dependence and toxicity. Many of them are illegal.
4. **Food additives:** It involves toxicity caused by additives used in formulation of food stuffs.
5. **Industrial chemicals:** It involves testing of toxicity or controlling exposure to those known to be toxic. **It is a large area of toxicological activity.**
6. **Naturally occurring substances:** Substances like phytotoxins, mycotoxins, and minerals, all occurring in the environment are considered in this category.
7. **Combustion products:** A large number of toxicants, generated primarily from fuels and other industrial chemicals are included in this category.

### 5.1.5 Regulatory Toxicology

It is concerned with the formulation of laws and regulations which are intended to minimise the effect of toxic chemicals on human health and the environment.

1. **Legal aspects:** It involves formulation of law and their regulations as well as enforcement by agencies like Food and Drug Administration (FDA), Environmental Protection Agency (EPA), or Occupational Safety and Health Administration (OSHA).
2. **Risk assessment:** It is the definition of risks, potential risks, and the risk-benefit equations necessary for the regulation of toxic substances. It is followed by risk communication and risk management.

## 5.2 DEFINITION AND BASIC KNOWLEDGE OF ACUTE, SUB-ACUTE AND CHRONIC TOXICITY

**Acute Toxicity**

Acute toxicity describes the adverse effects of a substance that result either from a single exposure or from multiple exposures in a short period of time (usually less than 24 hours). To be described as acute toxicity, the adverse effects should occur within 14 days of the administration of the substance.

It is widely considered unethical to use humans as test subjects for toxicity research. However some information can be gained from investigating accidental human exposures (eg factory accidents). Otherwise most acute toxicity data comes from animal testing or, more recently, in vitro testing methods and inference data on similar substances.

There are some regulatory values and experimental values related to acute toxicity. They are listed below:

**Regulatory Values:**

- **Threshold limit value-time-weighted average:** The maximum concentration to which a worker can be exposed every work day (8 hours) and experience no adverse health effects.
- **Short term exposure limit (STEL)/threshold limit value-short term exposure limit (TLV-STEL):** The concentration which no person should be exposed to for more than 15 minutes during an 8-hour work day.
- **Ceiling value (CV) or threshold limits value-ceiling (TLV-C):** The concentration which no person should ever be exposed to.

**Experimental Values:**

- No- observed-adverse-effect level (NOAEL)
- Lowest-observed-adverse-effect level (LOAEL)
- Maximum tolerable concentration ($MTC/LC_0$); maximum tolerable dose ($MTD/LD_0$)
- Minimum lethal concentration ($LC_{min}$); minimum lethal dose ($LD_{min}$)
- Median lethal concentration ($LC_{50}$); median lethal dose ($LD_{50}$); mediam lethal time ($LT_{50}$)
- Absolute lethal concentration ($LC_{100}$); absolute lethal dose ($LD_{100}$)

The most referenced value in the chemical industry is the median lethal dose or $LD_{50}$. This is the concentration of a substance which results in death of 50% of test subjects (typically mice or rats) in the laboratory. Lower the value of $LD_{50}$, higher is the toxicity of a substance. Conversely, higher the value of $LD_{50}$, lesser is the toxicity of a substance.

**Subacute Toxicity:**

When the substance is exposed for a period of 1-2 weeks, the observed effects are termed as sub-acute toxicity.

**Chronic Toxicity:**

The development of adverse effects as a result of long term exposure to a contaminant or other stressor is important in toxicology. Chronic toxicity is the one which is observed with a long term exposure of the substance (months or years). Adverse effects associated with chronic toxicity can be directly lethal but are more commonly observed as sub-lethal, including changes in growth, reproduction, or behaviour. Various toxicity tests can be performed to assess the chronic toxicity of different contaminants and usually lasts atleast 10% of an organism's life span. Results of aquatic chronic toxicity tests can be used to determine water quality guidelines and regulations for protection of aquatic animals.

Results from chronic toxicity tests can be used to calculate values that can be used for determining water quality standards. Chemical and biological factors are likely to influence chronic toxicity.

## 5.3 DEFINITION AND BASIC KNOWLEDGE OF GENOTOXICITY

Genotoxicity describes the property of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. Genotoxicity is often confused with mutagenicity. It is to be noted that all mutagens are genotoxic, while not all genotoxic substances are mutagenic. The alteration can have direct or indirect effects on the DNA: the induction of mutations, mistimed event activation, and direct DNA damage leading to mutations. The permanent, heritable changes can affect either somatic cells of the organism or germ cells to be passed on to future generations. Cells prevent expression of the genotoxic mutation by either DNA repair or apoptosis; however the damage may not always be fixed leading to mutagenesis.

### 5.3.1 Carcinogenicity

A carcinogen is a substance, radionuclide, or radiation which promotes carcinogenesis i.e. the formation of cancer. This may be due to the ability to damage genome or cause disruption of cellular metabolic processes. Common examples of non-radioactive carcinogens are inhaled asbestos, certain dioxins, and tobacco smoke. Tobacco smoke contains benzo(a)pyrine, tobacco specific nitrosamines like nitrosonornicotine, and reactive aldehydes like formaldehyde, which is a hazard in preparing plastics. Vinyl chloride, from which plastic PVC is manufactured, is also a carcinogen. There are many natural carcinogens like Aflatoxin $B_1$ produced by the fungus *Aspergillus flavus* growing on stored grains, nuts and peanut butter. Certain viruses like hepatitis B and human papilloma virus are also

carcinogens. Other infectious organisms like *Helicobacter pylori* and helminths like *Opisthorchis viverrni* and *Clonorchis sinensis* are also carcinogens.

Carcinogens may increase the risk of cancer by altering cellular metabolism or damaging DNA directly in cells, which interferes with biological processes and induces the uncontrolled, malignant division, ultimately leading to the formation of tumours. Co-carcinogens are chemicals that do not necessarily cause cancer on their own, but promote the activity of other carcinogens in causing cancer.

The International Agency for Research on Cancer (IARC) is a part of the World Health Organisation (WHO) of the United Nations. IARC classifies carcinogens as follows:

**Group 1:** The agent (mixture) is definitely carcinogenic to humans.

**Group 2A:** The agent (mixture) is probably carcinogenic to humans.

**Group 2B:** The agent (mixture) is possibly carcinogenic to humans.

**Group 3:** The agent (mixture or exposure circumstance) is not classifyable as to its carcinogenicity to humans.

**Group 4:** The agent (mixture) is probably not carcinogenic to humans.

Lung cancer, breast cancer, colon cancer and stomach cancer are the most commonly observed cancers world wide.

### 5.3.2 Teratogenecity

Teratogenecity refers to developmental toxicity and includes all manifestations of abnormal development of the foetus during pregnancy caused by environmental insult. It includes growth retardation, delayed mental development or other congenital disorders. Teratogens are substances that may cause birth defects via a toxic effect on an embryo or foetus.

Causes of teratogenecity can be broadly classified as follows:

- Toxic substances such as drugs in pregnancy and environmental toxins in pregnancy.
- Potassium iodide is a possible teratogen. Chronic exposure can have adverse effects on the thyroid.
- Vertically transmitted infection: infection transmitted from mother to foetus.
- Lack of nutrients: lack of folate during pregnancy causes spina difida. As an illustration, a list of drugs associated with folate antagonism with a likelihood of teratogenecity is as follows: Carbamazepine, Cholestyramine, Cyclosporine, Lamotrigine, Metformin, Methotrexate, Phenobarbital, Phenytoin, Primidone, Valproic acid and Triamterene.
- Physical restraint: Potter syndrome due to oligohydramnios in humans.
- Genetic disorders.
- Alcohol consumption during pregnancy.

During 1960s, a drug named Thalidomide was consumed by > 10,000 mothers, mostly in Europe. It was noted later that Thalidomide was a teratogen. More than 10,000 babies with

deformed organs, called as phocomelia were born, some of whom are still alive. Later on, testing for teratogenecity in animals has been made mandatory by regulatory authorities all over world. Only if the drug is not teratogenic in animals, it is given to human being during clinical trials.

### 5.3.3 Mutagenicity

Mutagen is a physical or chemical agent which changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level. Some of the mutagens can cause cancer and are likely to be carcinogens. All mutations do not cause cancer. Effects caused by mutagens are termed as mutagenicity.

Mutagens are of two types: physical mutagens and DNA-reactive chemicals.

**Physical Mutagens:**

Ionising radiations like X-rays, Y-rays and α-particles cause DNA breakage and other damages. The most common sources are Cobalt-60 and Cesium-137. Ultraviolet radiations with wavelength >260 nm are absorbed strongly by bases, producing pyrimidine dimmers and cause mutagenicity.

**DNA reactive chemicals**

A large number of chemicals may interact directly with DNA. Some of them are listed below:

- Reactive Oxygen Species (ROS): eg superoxide, hydroxyl radicals and hydrogen peroxide. A number of mutagens may generate ROS. These ROS may result in production of many base adducts, as well as DNA strand breaks and cross links.
- Deaminating agents: eg: nitrous acid causes transition mutations by converting cytosine to uracil.
- Polycyclic Aromatic Hydrocarbons (PAH), when activated to diol-epoxides can bind to DNA.
- Alkylating agents like ethylnitrosouria. These compounds transfer methyl or ethyl group to bases or the backbone phosphate groups of DNA. Nitrosamines are mutagens found in tobacco which are also carcinogens. Other alkylating agents include mustard gas and vinyl chloride.
- Aromatic amines and amides are mutagens. 2-acetylaminofluorene, found in cooked meat may cause cancer of the bladder, liver, ear, intestine, thyroid and breast.
- Alkaloid from plants like Vinca species can be converted into active mutagen or carcinogen.
- Bromine and some compounds containing bromine are mutagens.
- Sodium azide, a component in many car airbag systems is a mutagen.
- Psoralen combined with UV radiation causes DNA cross linking and hence chromosome damage.
- Benzene, an industrial solvent, synthetic rubber and some dyes are mutagenic.

- Intercalating agents like ethidium bromide and proflavin are mutagens.
- Metals like arsenic, cadmium, chromium and nickel are mutagens.

Mutagenicity can be tested by use of bacteria, yeast and drosophila. Some plant assays, cell culture assays, chromosome check systems and animal test systems are used to test mutagenicity. A commonest bacterial test, called as **Ames test** uses *Salmonella typhimurium* strains deficient in histidine biosynthesis for testing mutagenicity.

## 5.4 GENERAL PRINCIPLES OF TREATMENT OF POISONING

General principles for the management of poisoning are as follows:

### 5.4.1 Resuscitation and Stabilisation

- Treat life threatening problems Do not become a casualty yourself.
- Personal protection to be considered at all times (gloves, mask, protective suits).
- Need for decontamination to be considered early.

The management of poisoned patients follows the same approach as the management of any other life threatening conditions with three additional considerations.

- Safety of the staff should be considered on priority. Decontamination of the victim reduces continued exposure of the victim to the toxin. The use of decontamination limits the spread of toxic chemicals, which could lead to closure of critical facilities such as emergency department due to secondary contamination.
- Resuscitation of the severely poisoned patient must take into account the potential drugs involved in the process. It helps in identifying the mechanism of toxicity. Wherever specific antidotes are available, they can be appropriately administered.
- It should be remembered that the patient with toxic exposure is in a dynamic state as continuous absorption of the drug may cause abrupt changes in the level of consciousness and circulatory changes. This may predispose the patient to respiratory difficulties including the risk of aspiration and haemodynamic instabilities. Vital signs like heart rate, respiratpry rate, blood pressure, oxygen saturation and telemetry should be continuously monitored. The risk benefits of the need for invasive procedures should be carefully weighed in the context of rapid deterioration in the patient's clinical condition.

### 5.4.2 Toxicological Diagnosis

In order not to miss toxic conditions, it is always advisable that clinicians should give consideration to a possible toxic cause in particular when the clinical presentation may not indicate a specific diagnosis. It is also important to consider toxicological conditions in the context of multiple victims arriving from a common site with a similar spectrum of clinical symptoms and signs.

Consideration should be given to following facts:

- Identify the toxic agent or class based on history and physical examination.
- History involves medication and products brought in from the scene.

- If medical records of any prescription are available, that will facilitate identifying the cause.
- Contacting patient's primary physician is desirable.
- Recognition of toxidrome is very important.

Establishing the specific toxin or toxins responsible for the poisoning is crucial to the management of the final outcome. Some examples of toxidromes are given in table 5.1 A and 5.1 B.

**Table 5.1 (A) : Sympathomimetic toxindrome**

| Signs and symptoms | Possible toxins |
|---|---|
| • Anxiety/delirium<br>• Hypertension<br>• Tachycardia<br>• Hyperpyrexia<br>• Mydriasis<br>• Diaphoresis | • Cocaine, Amphetamine, Phencyclidine (PCP), Lysergic acid Diethylamide (LSD)<br>• Withdrawal from narcotics, Benzodiazepine, Alcohol, long term beta blocker therapy |

**Table 5.1 (B) : Cholinergic toxindrome**

| Signs and symptoms | Possible toxins |
|---|---|
| • Salivation<br>• Lacrimation<br>• Urinary incontinence<br>• Defaecation<br>• Gastric cramping, hypermotility<br>• Emesis | • Organophosphate compounds<br>• Carbamate insecticides |

Once poisoning is suspected or confirmed, a through evaluation of the patient is in line comprising a detailed history, physical examination and targeted investigations. Necessary follow-up is mentioned below.

**Clinical evaluation of the poisoned patient:** The clinical evaluation has the primary objective of classifying the patient into mild, moderate and severe categories of poisoning by obtaining a targeted history, performing a careful examination and specific laboratory investigation.

**History:** It should address to following issues:

1. Fact finding mission: Look for empty packets, vomitus with pill fragments.
2. Who was exposed?: Demographic information including age, sex and weight.
3. What was ingested?: Name of agent and type of formulation, eg tablet/liquid; composition and concentration of the content.
4. What else was ingested? : Any other co-ingestant like alcohol, traditional medications and health supplements.

5. How much exposure?: Estimate in mg/Kg body weight; for cutaneous exposure: expose body surface area.
6. When did poisoning occur?: Exact timing of ingestion or timings of ingestion episodes.
7. What were the symptoms post exposure?
8. How was patient exposed to toxin?: Route of exposure: oral, inhalation, cutaneous or injection. For cutaneous exposure: Duration of exposure.
9. Why was he/she exposed?: The reason for toxic exposure: Accidental/intentional; occupational exposure requires notification to Government.
10. AMPLE history?: A: Allergies (history); M: medications; P: past medical problems; L: last meal and drink; E: events that lead to poisoning.

**Examination:**

(a) Use all your senses to search for the clues:

- Look for track marks in cubital fossa and groin suggestive of IV drug abuse.
- Look for residue deposits around mouth, nose, body surface.
- Look for unusual colour of vomitus, urine.
- Feel temperature, sweating.
- Smel for alcohol and other unique odours.

(b) Assess ABCDE:

- **AB: Airway and breathing:** Ability to protect airway, respiratory rate and depth, oxygen saturation.
- **C: Circulation:** Pulse rate and regularity, blood pressure.
- **D: Disability:** Pupil size and equality, random glucose to exclude hypoglycaemia.
- **E: Exposure:** look out for external evidence of trauma like head injury.

**Toxicological Investigation:**

Targeted investigations should be done with following objectives:

(a) Assisting in confirming the diagnosis.
(b) Helping to predict severity of poisoning and prognosis.
(c) Helping to determine the need for more intensive treatment.
(d) Allowing correction of baseline fluid, electrolyte and acid base status.

Some useful investigations are mentioned below:

1. Random bedside glucose
2. ECG (electrocardiogram)
3. Serum electrolytes and renal function
4. Liver function tests (LFT)
5. Creatine kinase
6. Full blood count

7. Clotting screen: PT/PTT/INR
8. Arterial blood gas
9. Specific toxin level, eg Digoxin, Salicylate, Lithium
10. Serum osmolarity and osmolarity gap
11. Abdominal X-ray for radiopaque toxins

**Comprehensive Toxicological Screening Tests:**

Routine toxicological screen of blood, urine and stomach washout contents is not recommended. Some important tests like blood alcohol level in drink driving cases are suggested.

## 5.4.3 Therapeutic Interventions for Poisoning

Before intervention, consider following questions:

1. Is the toxic exposure potentially life threatening?
2. Does the procedure improve the final clinical outcome?
3. Does the benefit of the procedure outway its risks?

It is to be noted that poisoning is a dynamic process. This may result in patient's condition; hence frequent sequential assessment should be carried out.

**Decontamination:**

It involves removal of toxins from portals of entry before absorption into the blood stream. It is relevant for oral, inhalational and dermal routes.

The method used for decontamination depends on route of poisoning:

- **Inhalational exposure:** Evacuation from toxic environment and provision of supplemental oxygen.
- **Dermal exposure:** Removal of contaminated clothing and shower or irrigation of affected site.
- **For eye exposure:** Removal of chemicals by irrigation of affected eye; upto 1 L of saline or till symptomatic improvement.
- **Oral exposure:** Including emesis, performing gastric lavage, activated charcoal, whole bowel irrigation, cathartics. Emesis is not usually recommended.

**Enhanced Elimination of Absorbed Toxins:**

It indicates use of intervention which attempt removal of toxins which have been absorbed and are circulating in blood stream or distributed to the tissue. They include following alternatives:

1. Multiple Dose Acitvated Charcoal (MDAC).
2. Alkaline diuretic.
3. Haemodialysis and Charcoal Haemoperfusion.
4. Plasma exchange.

**Antidotes:** Specific antidotes are available only in limited cases. Sometimes use of antidotes may worsen the condition, eg combined poisoning with tricyclic antidepressants and Benzodiazepine may increase the risk of toxicity with use of Flumazenil (Benzodiazepine antagonist).

### 5.4.4 Supportive Care

Supportive care and observation may be necessary in poisonings to help evaluate delayed effects of some poisons, to manage an underlying disease which has been exacerbated due to overdose and to evaluate and treat complications. Following facts should be taken into account:

1. Vital signs.
2. Fluid/electrolyte/acid base status.
3. Delayed effects of poisoning.
4. Monitor and treat secondary complications.
5. Follow up for end organ damage.

Severity of intoxication, anticipation of potential serious toxic effects and the need for invasive therapeutic and supportive measures should also be considered.

### 5.4.5 Psychosocial and Workplace Safety Interventions

In case of intentional exposure, psychosocial support and counselling are important in prevention of poisoning at the community level. Following psychosocial considerations form part of the management plan and disposition of all patients with toxic exposures:

- Referral to medical social worker (MSW) for counselling.
- Psychiatric referral and followup.
- Workplace accidental reporting to appropriate Govenrmment authority.

Case of mass poisoning by contamination of methyl alcohol along with ethyl alcohol may need psychosocial interventions.

## 5.5 CLINICAL SYMPTOMS AND MANAGEMENT

### 5.5.1 Barbiturates

Clinically, barbiturates are used as sedatives/hypnotics. Their major action is production of sedation, hypnosis or anaesthesia through depression of CNS. The effect depends on the dose, mental status of the patient or individual at the time of ingestion, duration of action of the drug, the physical environment while under the influence, and tolerance of the individual to barbiturates.

The prototype structure of barbiturates is presented in Fig. 5.2.

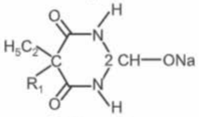



**Fig. 5.2**

**Toxicokinetics**

As indicated in figure 5.2, an increase in the number of carbons and bulkier side chains result in enhanced lipid solubility, with a corresponding increase in toxicity.

Barbiturates are largely non-ionic, lipid soluble compounds, and their $pK_a$ ranges between 7.2 and 7.9. Rapid movement into and out of CNS appears to determine rapid onset and short duration. Barbiturates with slowest onset and longest duration of action contain the most polar side chains (ethyl and phenyl with Phenobarbital structure). Table 5.2 indicates toxic concentrations of various barbiturates.

**Table 5.2 : Properties of barbiturates with respect to toxicity**

| Name | $R_1^*$ | Classification | Toxic concentration (mg/dl) | Half-life (hours) | $pK_a$ |
|---|---|---|---|---|---|
| Barbital | Ethyl | LA | 6-8 | – | 7.8 |
| Phenobarbital | Phenyl | LA | 4-6 | 24-40 | 7.2 |
| Amobarbital | Isopentyl | IA | 1-3 | 8-42 | 7.8 |
| Pentobarbital | 1-mb | SA | 0.5-1.0 | 16-48 | 7.9 |
| Secobarbital | 1-mb | SA | 0.5-1.0 | 20-34 | 7.9 |
| Thiopental | 1-mb, $C_2$ = S | UA | < 0.5 | < 1 | 7.4 |

$R_1^*$ = side group in figure 5.1; 1-mb = 1-methyl butyl; LA = long acting; IA = intermediate acting; SA =short acting; UA = ultrashort acting

Structure in Table 5.2 indicates that Phenobarbital enters and leaves the CNS very slowly as compared to the more lipophilic thiopental. In addition, the lipid barriers to drug metabolising enzymes lead to a slower metabolism for more polar barbiturates, considering that Phenobarbital is metabolised to the extent of 10% per day. Similarly, distribution in biological compartments, especially CNS, is governed by lipid solubility.

**Mechanism of Toxicity:**

CNS depression accounts for all of the toxic manifestations of barbiturate poisoning. The drugs bind to an allosteric site on the GABA-Cl ionophore complex (Y-aminobutyric acid), an inhibitory neurotransmitter, in presynaptic or post synaptic neural terminals in the CNS. This complex formation prolongs the opening of the chloride channel. Ultimately, by binding to $GABA_A$ receptors, barbiturates diminish the action of facilitated neurons and enhance the action of inhibitory neurons. Barbiturates stimulate the release of GABA at sensitive synapses. Thus the chemicals have GABA-like effects by decreasing the activity of facilitated neurons and enhancing inhibitory GABA-ergic neurons.

Two major consequences account for the toxic manifestations:

1. Barbiturates decrease post-synaptic depolarisation by acetyl choline, with ensuing post-synaptic block, resulting in smooth, skeletal and cardiac muscle depression.

2. At higher doses, barbiturates depress medullary respiratory centres, resulting in inhibition of all three respiratory drives.

The neurogenic drive, important in maintaining respiratory rhythm during sleep, is initially inhibited. Interference with carotid and aortic chemoreceptors and pH homeostasis disrupts the chemical drive. Lastly, interruption of carotid and aortic baroreceptors results in a decreased hypoxic drive for respiration. Thus, with increasing depth of depression of the CNS, the dominant respiratory drive shifts to the chemical and hypoxic drives.

**Signs and Symptoms of Acute Toxicity**

Signs and symptoms of barbiturate poisoning are related directly to CNS and cardiovascular depression. Reactions are dose- dependent and vary from mild sedation to complete paralysis. Clinical signs and symptoms are more reliable indicators of clinical toxicity than plasma concentrations. This is especially true when the CNS depression does not correlate with plasma concentrations, an indication that other CNS depressants may be involved.

At higher doses, blockade of sympathetic ganglia triggers hypotension, bradycardia and decreased ionotropy, with consequent decreased cardiac output. In addition, inhibition of medullary vasomotor centres induces arteriolar and venous dilation, further complicating the cerebral hypoxia and cardiac depression. Respiratory acidosis results from accumulation of carbon dioxide, shifting pH balance to the formation of carbonic acid. The condition resembles alcoholic inebriation as the patient presents with hypoxic shock, rapid but shallow pulse, cold and sweaty skin (hypothermia), and either slow, or rapid, shallow breathing.

**Clinical Management of Acute Overdose:**

Treatment of overdose is symptomatic. It includes maintaining adequate ventilation, keeping the patient warm, and supporting vital functions. Oxygen support, forced diuresis, and administration of volume expanders has been shown to maintain blood pressure and adequate kidney perfusion and prevent circulatory collapse. If fewer than 24 hours have elapsed since ingestion, gastric lavage, induction of emesis by Apomorphine, delivery of saline cathartic or administration of activated charcoal, enhances elimination and decreases absorption. In particular, multidose activated charcoal (MDAC) increases the clearance and decreases the half-life of Phenobarbital. Alkalinisation of urine to a pH of 7.5-8.0 increases clearance of long-acting barbiturates, while short- and intermediate- acting compounds are not affected by changes in urine pH.

If renal or cardiac failure, electrolyte abnormalities, or acid-base disturbances occur, then haemodialysis is recommended. Although most cases of Phenobarbital overdose respond well to cardiopulmonary supportive care, severe cases require haemodialysis or charcoal haemoperfusion. Neither of these procedures will remove significant amounts of short- or intermediate- acting barbiturates. Through ion exchange, haemodialysis is more effective in removing long-acting barbiturates than short-acting compounds because there is less protein and lipid binding of long-acting barbiturates. If renal and cardiac functions are

satisfactory, alkalinisation of urine and plasma with sodium bicarbonate promotes ionisation of the acidic compounds. This procedure hastens their excretion, provided that reabsorption and protein and lipid binding are minimised. Incorporation of CNS stimulants or vasopressors is not recommended.

Even with complete recovery, complications affect prognosis. This includes the development of pulmonary oedema and broncho-pneumonia, infiltration with lung abscesses, and renal shut down.

**Tolerance and Withdrawal:**

Pharmacodynamic tolerance contributes to the decreased effect of barbiturates, even after a single dose. With chronic administration of gradually increasing doses, pharmacodynamic tolerance continues to develop over a period of weeks to months, as the homeostatic feedback response to depression is activated in the presence of barbiturates.

Pharmacokinetic tolerance contributes less to the development of tolerance. Enhanced metabolic transformation and induction of hepatic microsomal enzymes ensues subsequent pharmacodynamic tolerance.

Sudden withdrawal of barbiturates from addicted individuals runs the risk of development of hallucinations, sleeplessness, vertigo, and convulsions, depending upon the degree of dependency.

## 5.5.2 Morphine

Morphine is a major alkaloid (10%) obtained from the milky exudates of unripe capsule of *Papaver somniferum L* (opium poppy). Depending on diurnal variations, the isolated latex undergoes alkaloid biosynthesis and metabolic destruction, which contribute to the variability in alkaloid composition of crude opium samples. The narcotic, antispasmodic, sedative, hypnotic and analgesic properties of the extract are known for a long time.

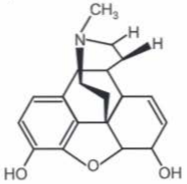



**Fig. 5.3**

The derivatives of morphine are collectively called as Opioids. The Opioids are composed of 6-membered saturated heterocyclic rings forming the phenanthrene nucleus to which is attached a piperidine ring. The structure represents the prototype (see Fig. 5.3) for all opioids except Methadone and Meperidine. Although opiate alkaloids exhibit a phenanthrene nucleus, the majority of derivatives have the isoquinoline ring structure. Esterification of the phenolic functions, such as in the formation of diacetylmorphine, results in a compound with increased lipid solubility and increased potency and toxicity.

**Mechanism of Toxicity:**

The mechanism of opiate toxicity is an extension of its pharmacology and is directly related to interaction with stereospecific and saturable binding sites or receptors in the CNS and other tissues. The opioid receptors are biologically active sites of several endogenous ligands, including the two pentapeptides, methionine-enkephalin and leucine-enkaphalin. Three receptor classes have been identified for morphine. They are as follows:

1. Compounds which selectively bind to the **mu-receptor (μ)** exhibit morphine-like analgesia, euphoria, respiratory depression, myosis, partial GI inhibition, and sedative effects.
2. Narcotic antagonists like Pentazocine, Nalorphine and Levorphanol bind to the **kappa-receptor (κ)**, although analgesia, sedation, delusion, hallucinations (psychotomimesis), GI inhibition, and mitotic effects still persist.
3. Pentzocine and Nalorphine are also known to have affinity for the **delta- receptors (δ)**, although this binding is primarily associated with dysphoria and mood changes (due to inhibition of Dopamine release).

**Toxicokinetics:**

Morphine is rapidly absorbed from an oral dose and from intramuscular and sub-cutaneous injections. Peak plasma levels occur at 15-60 minutes and 15 minutes respectively. Morphine is metabolised extensively with only 2-12% excreted as the parent molecule, while 60-80% is excreted in urine as conjugated glucuronide. Heroin is rapidly metabolised, first to monoacetylmorphine and then to morphine. Both heroin and monoacetylmorphine disappear rapidly from the blood with a half-life of 3 minutes, 5-10 minutes respectively. The morphine levels rise slowly, persist longer and decline slowly. About 10-15% Codeine is demethylated to form morphine and norcodeine conjugates.

**Signs and Symptoms of Clinical Toxicity:**

Clinical signs and symptoms correlate with the highest concentrations of binding sites in CNS and other tissues. Particularly, the limbic system (frontal and temporal cortex, amygdala and hippocampus), thalamus, corpus striatum, hypothalamus, mid-brain and spinal cord have the highest concentration. Analgesia affects spinal, ascending and descending tracts, extending upto the medullary raphe nuclei (mid-brain). Effects on mood, movement, and behaviour correlate with interaction with receptors in the globus pallidus (basal ganglia) and locus ceruleus, while mental confusion and euphoria alter neuronal activity in the limbic system. Hypothalamic effects are responsible for hypothermia. Myosis is due to stimulation of μ-receptor.

The clinical presentation of opioid triad is characterised by CNS depression (coma), myosis and respiratory depression. Myosis suggests that the patient is still responsive. Respiratory depression is a result of depressed brain stem and medullary respiratory centres responsible for maintainance of normal rhythm. μ-receptor agonists depress respiration in a dose-dependent manner and can lead to respiratory arrest within minutes. 50% of acute opioid overdose is accompanied by a frothy, non-cardiogenic, pulmonary oedema,

responsible for majority of deaths. The condition involves loss of consciousness and hypoventilation, resulting from hypoxic, stress-induced, pulmonary capillary fluid leakage. Peripheral effects include bradycardia, hypotension and decreased GI motility. Urine output also diminishes due to increased secretion of antidiuretic hormone (ADH).

**Clinical Management of Acute Overdose:**

Maintenance of vital functions, including respiratory and cardiovascular integrity, is of paramount importance in the clinical management of acute opioid toxicity. Gastric lavage and induction of emesis are effective if the treatment is instituted soon after ingestion. It is possible to reverse the respiratory depression with opioid antagonists.

**Naloxone** is a pure opioid antagonist available as an injectable. A 2-mg bolus repeated every 5 minutes, followed by 0.4 mg every 2-3 minutes as needed (upto 24 mg total), dramatically reverses the CNS and respiratory depression. Depending on the extent of narcotic overdose, a continuous infusion of Naloxone may be required, especially in the presence of opioids with longer half-life, such as Propoxyphene or Methadone. As respiration improves, Naolxone, which has a half-life of 60-90 imnutes, may be discontinued and resumed as necessary. If there is no response after 10 mg of Naloxone, concomitant ingestion with other depressants is likely. Naloxone is of limited benefit in reversing non-cardiogenic pulmonary oedema.

**Naltrexone** is a pure opioid antagonist available as oral tablet. A 50-mg dose of Naltrexone blocks the pharmacological effects of opioid by competitive binding at opioid receptors. It is also indicated in the treatment of alcohol dependence. Naltrexone has been noted to induce hepatocellular injury when given in excess.

**Nalmefene,** available in 100 µg/ml and 1 mg/ml ampoules, is indicated for the complete or partial reversal of natural or synthetic opioid effects. It is a 6-methylene analogue of Naltrexone. Nalmefene is associated with cardiac instability, although it is due to abrupt reversal of opioid toxicity.

Decontamination with activated charcoal, gastric lavage, high dose continuous infusion with Naloxone, and emergency management of toxicity in anticipation of a developing opioid syndrome are desirable.

**Tolerance and Withdrawal:**

**Addiction** with morphine involves compulsive psychoactive drug use with an overwhelming involvement in securing and using opioid drugs. If the drug is suddenly withdrawn, then withdrawal syndrome is observed; it involves specific symptoms. **Compulsive drug use** involves the psychological need to procure and use drugs, often called as "craving". In this case, the uncontrollable drive to obtain the drugs is necessary to maintain an optimum state of well-being. **Habituation** refers to psychological dependence. **Physical/physiological dependence** involves the need for repeated administration in order to prevent withdrawal/abstinence syndrome. With repeated chronic dosing, seizure threshold for opiate narcotics is elevated, threatening with all opioids, regardless of category.

The complex phenonmena of **tolerance** requires the satisfaction of several criteria. With repeated administration addicted individuals need greater amounts of drug in order to achieve the desired effect. The effect is markedly diminished with continued use of the same amount of drug. Since various pharmacological effects on different organ systems are not uniformly distributed, tolerance is not evenly demonstrated. While a diminished euphoric effect continues with progressive tolerance, the increasing doses threaten respiratory depression. Increased metabolism, adjustment to the sedative, analgesic and euphoric effects are proposed as possible mechanisms for the development of tolerance – i.e., the physiological drive to achieve homeostasis.

Depending on the drug, the withdrawal syndrome is precipitated hours after the last narcotic dose with peak intensity occurring at about 72 hours. Although the withdrawal syndrome is rarely fatal, administration of an opioid at any time during withdrawal corrects the condition.

**Clinical Management of Addiction:**

Characterisation of the opioid withdrawal syndrome is presented in Table 5.3.

**Table 5.3: Characterisation of the opoid withdrawal syndrome**

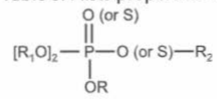
| Stage | Time after last dose | Signs and symptoms |
|---|---|---|
| Anticipatory | 3-4 hours | Withdrawal, fear, craving, compulsive drug seeking behaviour. |
| Early withdrawal | 8-12 hours | Lacrimation, sweating, listless behaviour, anxiety, restlessness, stomach cramps. |
| Early withdrawal | 12-16 hours | Restless sleep, nausea, vomiting, mydriasis, anorexia,tremors, cold clammy skin, fever, chills, compulsive drug seeking behaviour. |
| Early withdrawal | 48-72 hours | Peak intensity; tachycardia, hypertension, hypothermia, piloerection, muscle spasms, continued nausea, vomiting, dehydration, compulsive drug seeking behaviour, risk of cardiovascular collapse . |
| Protracted abstinence | 6 months | Stimulus-driven cravings, anorexia, fatigue, bradycardia, hypotension. |

**Names of Morphine Derivatives:**

Following derivatives of morphine share drug dependent behaviour: Codeine, Diphenoxylate, Fentanyl, Meperidine, Pentazocine, Propoxyphene, Hydrocodone/Oxycodone, Tramadol, Clonidine.

### 5.5.3 Organophosphorous Compounds (Organophosphates, OP)

The structural core of organophosphates (OP) contains a central phosphate nucleus to which various aliphatic side chains are attached. The prototype structure is given in Fig. 5.4. In this structure, $R_1$ is a methyl or ethyl group and $R_2$ is an aliphatic or aromatic side chain. Most of these compounds are dense liquids (specific gravity above 1.25) or solids at room temperature, have low vapour pressure, and are slightly soluble or insoluble in water. The sulphur containing compound like Dimethoate, requires metabolic activation prior to binding to the enzymatic target. Table 5.4 lists properties and toxicity of OPs.




$R_1$ = Methyl or ethyl group
$R_2$ = Aliphatic or aromatic hydrocarbon side chain

**Fig. 5.4**

**Table 5.4: Names, physical properties and oral $LD_{50}$ values (in rodents) of OPs**

| Common name | Chemical name/synonym | Physical characteristics | Rodent $LD_{50}$ in mg/Kg |
|---|---|---|---|
| TEPP | Tetraethyl pyrophosphate | Liquid, agreeable odour, miscible in water and organic liquids. | 1.1 |
| Disulfoton | Phosphorodithioic acid O, O-diethyl ester | Colourless oil, immiscible in water. | 2.3-6.8 |
| Mevinphos | Phosdrin | Yellow liquid, miscible with water. | 3.7-6.1 |
| Parathion ethyl | Paraphos, Thiophos | Pale yellow liquid, practically insoluble in water. | 3.6-13 |
| Azinophos methyl | Guthion | Crystalline solid, soluble in alcohols and organic liquids. | 11 |
| DDVP | Dichlorvos | Non-flammable liquid, miscible with water and organic liquids. | 56-80 |
| Chlorpyrifos | Dursban, Lorsban | White crystals, miscible with alcohol and organic liquids. | 145 |
| Dimethoate | Cygon, Roxion | Sulphur containing crystals, slightly soluble in water. | 250 |
| Malathion | Malamar 50, Cythion | Brown-yellow liquid, slightly soluble in water, miscible in organic liquids. | 1000-1375 |
| Ronnel | Fenchlorphos, Ectoral | White powder, insoluble in water, miscible in organic liquids. | 1250-2630 |

OPs are popular chemicals used as household and agricultural insecticides. Their wide distribution as industrial chemicals allows access to the general population. Hence they constitute a public health hazard due to suicidal tendency with them. They are most rapidly absorbed after inhalation, especially when delivered in aromatic hydrocarbon vehicular solvents.

**Mechanism of Toxicity:**

Acetyl choline (ACh) is a neurotransmitter found throughout the central , autonomic and somatic nervous systems. Specially, ACh receptors are located at autonomic preganglionic sympathetic nicotinic and parasympathetic muscarinic synapses, autonomic post ganglionic muscarinic parasympathetic synapses, somatic neuromuscular cholinergic synapses, and central cholinergic synapses. ACh activity is either terminated or potentiated by alteration of metabolism at cholinergic synapses, principally through interference with reuptake or enzymatic degradation. In the enzymatic pathway, the enzyme acetylcholinesterase, either true or pseudo, is predominantly distributed amongst RBCs, central, somatic and autonomic neurons, grey matter of the brain, spinal cord, lung and spleen. Pesudocholinesterase (plasma cholinesterase) is located in serum, plasma, white matter, liver, pancreas and heart tissue.

ACh forms an ester link with the anionic site of the enzyme, and is subsequently hydrolysed to inactive components according to reactions shown in Fig. 5.5.

1. Ach + AchE → Ach – AchE complex
2. Ach – AchE complex → Choline + Acetyl – AchE
3. Acetyl – Ache + $H_2O$ → Acetic acid + AchE

**Fig. 5.5: Sequence of events during Ach + AchE interaction**

These reactions are reversible in nature and the active enzyme is subsequently regenerated.

OPs inhibit the action of acetyl cholinesterase by phosphorylating the active esteratic site, forming an irreversible OP-ACh enzyme complex, rendering it incapable of hydrolysing ACh. Thus, inhibition of the enzyme results in an accumulation and overstimulation of ACh at autonomic and somatic receptors. The irreversible nature of the complex requires days to weeks for disassembly. In addition, phosphorylation prompts the enzyme to undergo an accelerated ageing process, where it looses an alkyl group and prevents it from spontaneous regeneration. These circumstances account for toxic manifestations of OPs.

**Signs and Symptoms of Acute Toxicity:**

Low doses of OP insecticides produce mild to moderate toxicity, depending on the remaining percentage of viable acetylcholinesterase activity. 20-50% of enzyme activity results in mild toxicity while 10-20% of remaining activity results in moderate toxicity. Acute initial toxic effects mimic exaggerated cholinergic muscarinic stimulation, including salivation, lacrymation, excessive sweating (diaphoresis), miosis, tachycardia, hypertension and bronchoconstricton. Higher doses cause overstimulation of both nicotinic and muscarinic

receptors, resulting in diarrhoea, urinary incontinence, bradycardia, muscle twitching, fatigue, hyperglycaemia, bronchospasm and bronchorrhea. Increased depolarisation at nicotinic neuromuscular synapses results in muscle weakness and flaccid paralysis.

CNS cholinergic stimulation suppresses central medullary centres resulting in depressed respiration, headache, anxiety, restlessness, confusion, psychosis, seizures, and coma. Death with OP poisoning is secondary to respiratory paralysis and cardiovascular collapse.

Acute pancreatitis, myocardial dysrrhythmias, and hydrocarbon pneumonitis following aspiration of the solvent vehicle are complications of OP poisoning. Although chronic effects from OP toxicity are limited, some latent pathology may develop. OP-induced delayed neuropathy (OPIDN) is a delayed syndrome. It is characterised by muscular weakness and paralysis of extremities, especially of hand and foot muscles, progressing to persistent spatic spinal paresis. The syndrome is either slowly reversible over several months or irreversible. Intermediate syndrome (IMS) is characterised by muscular paralysis innervated by cranial nerves. It is associated with excessive exposure to OPs and results in prolonged acetylcholinesterase enzyme inhibition at the neuromuscular junction. Prevention or recovery from development of IMS is achieved by early therapy following OP exposure.

**Clinical Management of Acute Poisoning:**

Decontamination, airway stabilisation, and activated charcoal are important initial supportive measures for OP intoxication. Washing dermal areas with a mild soap, removal of contaminated clothes, and rinsing the eyes is necessary for dermal or ocular exposure. Atropine and Pralidoxime (2-PAM) follow as specific OP antidotes.

Atropine is a competitive antimuscarinic cholinergic antagonist at central and peripheral autonomic receptors. It has no effect on neuromuscular or nicotinic receptors. In adults, Atropine, in an intravenous dose of 1-2 mg counteracts the excessive bronchial and autonomic secretions and normalises heart rate. The dose is repeated every 5-10 minutes, depending on improvement of respiration.

2-PAM is a quarternary amine of the oxime class which reactivates acetylcholinesterase by severing the OP-acetylcholinesterase covalent bond at nicotinic, muscarinic, and central cholinergic sites. Pralidoxime is most effective when administered soon after exposure, before the poisoned enzyme complex has aged and becomes resistant to the effects of the antidote. The drug also scavenges remaining OP molecules, has few adverse reactions, and its action is synergistic with Atropine. An initial dose of 1-2 gm, by continuous IV infusion is followed by 500 mg/hour for 24 hours, in order to maintain effective therapeutic levels of 4 muμg/L.

## 5.5.4 Lead Poisoning

Lead is available in abundance in the Earth's crust; its compounds are widely distributed throughout the world. The principal ores are Galena (sulphide form), Cerussite, and Angelsite. The main use of lead is in the production of storage batteries and sheathing electric cables. It is also useful as protective shielding from X-rays and radiation from nuclear reactors. Lead compounds are commonly used as pigments in paint, putty, ceramic and insecticides. It was

incorporated as additive in gasoline; however it has been banned because it is an environmental pollutant. Some of the indeginous/herbal medicines have been reported to contain high amounts of lead.

**Mechanism of Toxicity:**

The mechanism of lead toxicity involves its ability to inhibit or mimic the action of calcium and to interfere with vital proteins by binding to sulfhydryl, amine, phosphate and carboxyl groups. Lead increases intracellular levels of calcium in brain capillaries, neurons, hepatocytes, and arteries which trigger smooth muscle contraction, thereby inducing hypertension.

Lead interferes with biosynthesis of heme by interfering with ferrochelatase, aminolevulinic acid synthetase (ALAS) and amino levulinic acid dehydrase (ALAD). Hence decreased haemoglobin and anaemia results in individuals exposed to excessive lead. Effects on heme synthesis impact renal and neurological parameters. In bone, lead alters circulating levels of 1,25-dihydroxyvitamin D, affecting calcium homeostasis and bone cell function. In the nervous system, lead substitutes calcium as a secondary messenger in neurons, blocking voltage-gated calcium channels, inhibiting influx of calcium and subsequent release of neurotransmitter. The result is inhibition of synaptic transmission. Lead inhibits glutamate uptake and glutamate synthetase activity in astroglia, thus inhibiting the regeneration of glutamate, a major excitatory neurotransmitter.

**Toxicokinetics:**

The bioavailability of lead is dependent on ingestion in the presence of food (10% or less) or after fasting (60-80%). Immediately following ingestion, lead is distributed widely to plasma and soft tissue; gets redistributed and accumulates in bone. In children, bone lead accounts for about 73% of total body burden, while in adults, it increases to 94% due to slower turnover rate of bone with age. Lead absorption is dependent on nutritional status. In children, iron deficiency correlates with higher blood levels of lead, suggesting that iron may affect lead absorption. A similar correlation is found with calcium levels. The rate of deposition of inhaled inorganic lead is about 30-50% but is largely dependent on the particle size and ventillatrion rate.

Lead, not retained in the body, is excreted primarily by the kidneys as soluble salts or through biliary clearance in the GI tract in the form of conjugates with organic compounds. Exhalation is also considered as a major excretion route of organic lead.

Distribution of lead is well characterised. Blood lead is found primarily in RBCs (99%); distribution occurs primarily to soft tissue. Liver, lung, spleen and kidneys have the highest concentrations, with redistribution resulting in high bone concentrations. Lead does not distribute routinely in bone, but will accumulate in those regions undergoing active calcification at the time of exposure.

Inorganic lead is not metabolised or biotransformed, but forms complexes with a variety of protein and non-protein ligands. Organic lead is metabolised in the liver by an oxidative dealkylation catalysed by cytochrome P450.

**Signs and Symptoms of Acute Toxicity:**

Exposure of excessive lead, through the GI tract or by inhalation, usually results in cramping, colicky abdominal pain and constipation. Severe abdominal pain is accompanaid by nausea, vomiting and bloody stools. Early symptoms of lead exposure include fatigue, apathy and vague GI pain. Arthralgias and myalgias of the extremities may also occur. Headache, confusion, stupor, coma, seizures, and optic neuritis are all manifestations of lead neurotoxicity. Upon further exposure, CNS symptoms like insomnia, confusion, impaired concentration, and memory problems become more pronounced. Lengthy exposure can present with a distal motor neuropathy, progressing to lead encephalopathy with seizures and coma. Reproductive problems, like infertility in men, spontaneous abortions, gouty arthritis and renal failure have been reported.

**Signs and Symptoms of Chronic Toxicity:**

Chronically exposed individuals develop anaemia and demonstrate pallor. Jaundice may be seen due to acute haemolysis. Examination of the gums may show a blue- grey pigmentation, or "lead-line".

**Treatment of Acute Poisoning:**

Parenteral administration of chelating agents, Dimercaprol and $CaNa_2$-EDTA, is used to reduce body burdens of absorbed lead. Penicillamine has been used as an oral chelating agent, although it is less effective in comparison to EDTA. In patients with kidney impairment, Dimercaprol is recommended, since excretion is primarily in bile rather than urine. EDTA mobilises lead from bone to soft tissue and may aggravate acute toxicity if not given in conjunction with Dimercaprol. DMSA (Succimer) is the only FDA-approved orally administered chelating agent for treating children with lead blood levels > 45 µg/dl.

**Clinical Monitoring:**

Since lead accumulates in RBCs rather than plasma, the method of choice for determination of lead exposure was the erythrocyte protoporphyrin (EP). The method is insensitive to lead levels in the range of 10-25 µg/dl; hence it is not recommended for tracking childhood lead poisoning. Since lead redistributes to bone, use of radiographic technique is useful for detection of "lead- lines".

## 5.5.5 Mercury Poisoning

Huge amount of mercury (> 10,000 tons) is discharged from burning coal, natural gas and refining of petroleum products. In addition, mercury is used in a number of products including thermometers, barometers, electrical apparatus, paints and pharmaceuticals. Some indeginous/herbal medicines have been reported to contain mercury.

Regardless of source, both organic and inorganic mercury undergoes environmental transformation. Conversion of inorganic mercury to methyl mercury results in its release from sediment at a relatively fast rate and leads to its wider distribution. Inorganic mercury may be methylated and demethylated by microorganisms. Elemental mercury at ambient air temperatures volatilises and is extremely dangerous.

**Occupational and Environmental Exposure:**

Methyl mercury released in the aqueous environment bio-accumulates in plankton, algae and fishes. In fishes, the absorption of methyl mercury is faster than inorganic mercury and its clearance is slower resulting in high menthyl mercury concentrations. Through fishes mercury enters the food chain.

The pollution of environment with mercury compounds leads to neurotoxicity and is referred as Minamata disease. Two poisonings, one in Minamata Bay (1956-1975) and Niigata (1964) occurred as a consequence of industrial releases of mercury compounds into Minamata Bay and Agano river. In addition, an outbreak occurred in Iraq (1971-1972), resulting from eating bread made from seed grain coated with a methyl mercury fungicide.

Most human exposure to mercury is by inhalation, because it readily diffuses across the alveolar membrane due to its lipid solubility. It has high affinity for RBCs and CNS.

**Mechanism of Toxicity:**

Mercury ion binds to thiol or SH groups of proteins. It results into inactivation of various enzymes and structural proteins and alters permeability of cell membrane. It contributes to severe toxicological effects. Increased oxidative stress, disruption of microtubule formation, interference with protein synthesis, DNA replication and calcium homeostasis are possible pathways of toxicity.

**Toxicokinetics:**

Inhaled mercury vapours are efficiently absorbed to the extent of 70-80%. Absorption of liquid metallic mercury is insignificant. The absorption rate for inorganic mercuric salts varies and is dependent on the chemical form. Oral absorption of organic mercury is nearly 100%.

For all forms of mercury, the highest accumulation is in kidney. Because of high lipophilicity of metallic mercury, transfer through the placenta and the blood-brain barrier is complete. Inorganic mercury compounds have a lower lipophilicity and their penetration in different organs is less effective.

Metallic mercury is oxidised to the divalent form by the catalase pathway, and the divalent form is reduced to the metallic form. Elimination occurs via urine, faeces, while organic mercury is eliminated primarily in the feces. Renal excretion of inorganic mercury increases with time. Both inorganic and organic forms are excreted in breast milk. A small fraction of mercury may be exhaled after exposure to mercury vapour. About 90% of methyl mercury is excreted in feces after acute or chronic exposure. Methyl mercury excretion does not increase with time.

**Signs and Symptoms of Acute Toxicity (Inhalation and Ingestion):**

Accidental acute exposure to high concentrations of metallic mercury vapour has resulted in human fatalities. The most common symptoms of inhalation are cough, dyspnoea, tightness and burning pain in the chest. GI effects include acute inflammation of oral cavity, abdominal pain, nausea, and vomiting. Increased heart rate and blood pressure are due to cardiovascular effects. Adverse renal effects result in proteinuria, haematuria and oilguria. Severe neurotoxic effects result in behavioural, motor and sensory disruptions.

Ingestion of inorganic mercurial salts causes severe GI irritation including pain, vomiting, diarrhoea, and renal failure. Contact dermatitis, hyperkeratosis, acrodynia (pink disease),

shock, and cardiovascular collapse are observed in patients with acute exposure to inorganic mercurial salts.

**Subacute or Chronic Toxicity:**

The major clinical symptoms of methyl mercury toxicity are neurologic and include paresthesia, ataxia, dysarthria and deafness. There may be a latency period of weeks or months from the time of exposure until the development of symptoms. Some pathological features include degeneration and necrosis of neurons in focal areas of occipital cortex and in the granular layer of the cerebellum. It results in damage due to mercury to small neurons in cerebellum and visual cortex.

**Treatment:**

For dermal or ocular exposure, washing of exposed areas is suggested. Reducing absorption from the GIT is relevant to inorganic forms. Oral administration of a protein solution reduces absorption of mercury, based on affinity for binding to SH groups. Administration of activated charcoal is used in case of acute high-dose situations. Gastric lavage and induction of emesis are also recommended. Emesis is contraindicated to mercuric oxide, due to its caustic nature.

To reduce body burden, chelation therapy is the treatment of choice. The chelator depends on the form of mercury, route of exposure, and possible side effects which are expected. BAL is one of the effective chelators for inorganic mercury salts, while D-penicillamine is marginally effective as a chelator for elemental and inorganic mercury.

## 5.5.6 Arsenic Poisoning

Arsenic (As) is a naturally occurring element. Organic forms are less toxic than the inorganic forms. Some organic compounds of arsenic are gases or low-boiling liquids at normal temperatures. Burning of arsenic, or contact with acid, results in production of Arsine, which is a deadly gas. More than 21 arsenic compounds are of concern based on their environmental presence.

Inorganic arsenic is found in ground water, surface water, and many foods such as rice and grains. Exposure is primarily through drinking water, but food also is considered as a significant source. Arsenic trioxide ($As_2O_3$) is a major ingredient of Traditional Chinese Medicine (TCM) and is used against acute promyelocytic leukaemia. Fowler's solution (potassium arsenite) has been used as a treatment for patients with asthma. Inorganic arsenic compounds are mainly used as wood preservatives, insecticides, herbicides and in the production of metal alloys.

**Mechanism of Toxicity:**

The toxicity is dependent on the chemical form and the oxidation state at the time of exposure. The physical state i.e. gas, solution, powder particle size and factors like rate of absorption into cells, elimination rate and the nature of chemical substituents determine the toxic outcome. The mechanism of arsenic toxicity is related to inactivation of key enzyme systems. Inorganic pentavalent arsenic does not react with enzymes directly; but it first reduces to trivalent arsenic before exerting toxic effects. It binds to –SH and –OH groups of the enzymes. Inactivation of pyruvate dehydrogenase with trivalent arsenic prevents generation of ATP. Arsenic inhibits succinic dehydrogenase activity and can uncouple

oxidative phosphorylation, a process which results in disruption of all cellular functions. Arsenic targets and accumulates within mitochondria.

**Toxicokinetics:**

Arsenate and arsenite are well absorbed by both oral and inhalation routes. It is methylated in the body by alternating reduction of pentavalent arsenic to trivalent arsenic. Most mammals metabolise arsenic to mehtylarsonic acid (MMA) and dimethylarsinic acid (DMA). MMA and DMA are readily excreted in urine and act as a detoxification mechanism. Increase in tissue concentrations result if methylation of arsenic is diminished. Glutathione and other thiols act as reducing agents in these reactions. In mammals, the liver is an important site for methylation of arsenic, especially following first passage through the liver. Arsenic is also methylated in other tissues like testes, kidney, liver and lungs.

**Signs and Symptoms of Acute Toxicity:**

Patients with acute exposure to arsenic experience GI distress characterised by nausea, vomiting, abdominal pain and profused watery or bloody diarrhoea. Death is common in patients who have ingested large doses. Serious respiratory effects such as pulmonary oedema, haemorrhagic bronchitis, and respiratory distress are seen with acute oral poisoning. Hypotension, tachycardia and complaint of metallic taste in the mouth and garlic odour on the breath, as well as delirium, are noted in patients with acute toxicity. Anaemia and leukopenia are common effects of acute arsenic poisoning in human beings. Acute arsine gas exposure is characterised by headache, nausea, vomiting, diarrhoea and abdominal pain. Dyspnoea and sever jaundice are also observed.

**Signs and Symptoms of Chronic Toxicity:**

Chronic arsenic toxicity is characterised by changes in skin pigmentation, plantar and palmar hyperkeratosis, GI symptoms, anaemia, skin cancers and liver disease. In patients treated with Fowler's solution, which contains potassium arsenite, non-cirrhotic portal hypertension is observed. Bone marrow depression results in anaemia and leukopenia, Raynaud's phenonmena, and acrocyanosis may also occur. Peripheral neuropathies have been reported. Nerve injury has been reported with Swedish copper smelter workers, chronically exposed to $As_2O_3$.

**Treatment:**

Delay or prevention of arsenic absorption in cases of high-dose oral exposure is treated by consumption of large volumes of water, gastric lavage, cathartics initiated within a few hours of exposure. Chelation therapy is indicated for acute arsenic poisoning by the use of BAL and D-penicillamine. Patients who are minimally symptomatic and have chronic arsenic poisoning may be removed from the source of their exposure without chelation therapy.

**Carcinogenesis:**

There is convincing evidence from epidemiological studies suggesting that inhalation exposure to inorganic arsenic compounds increases the likelihood of developing lung cancer. Most cases involve inhalation of arsenic trioxide by workers at copper smelting plants, resulting in a significant increase in respiratory cancer mortality. The likelihood that ingestion of inorganic arsenic results in increased risk of skin cancers and basal cell carcinoma have been noted. Tobacco smoke is known to contain arsenic and is one of the reasons for cancer caused by tobacco.

## 5.6 CHRONOPHARMACOLOGY

### 5.6.1 Definition of Rhythm and Cycles

A biological rhythm is any cyclic change in the level of a bodily chemical or function. Biological rhythms are of two types: internal (endogenous) and external (exoenous). Internal rhythms are controlled by the internal biological clock eg. body temperature cycle. External rhythms are controlled by synchronising internal cycles with external stimuli eg. sleep/wakefulness and day/night. The external stimuli include environmental time cues like sunlight, food, noise or social interaction.

### 5.6.2 Biological Clock and its Significance

Biological rhythms are of four types: circadian rhythms, diurnal rhythms, ultradian rhythms and infradian rhythms.

**Circadian** rhythms are endogenously generated rhythms with a period close to 24 hours.

**Diurnal** rhythms are circadian rhythms which are synchronised with the day/night cycle.

**Ultradian** rhythms are biological rhythms (eg feeding cycles) with a period much shorter than that of a circadian rhythm.

**Infradian** rhythms are biological rhythms with a cycle of more than 24 hours eg. the human menstrual cycle.

The word circadian is derived from a Latin phrase meaning "about a day" (circa means about and dia means a day). Circadian rhythms are physiological and behavioural rhythms and include:

- Sleep/wakefulness cycle
- Body temperature
- Patterns of hormone secretion
- Blood pressure
- Digestive secretions
- Levels of alertness
- Reaction times

Circadian rhythms have a period of approximately 24-25 hours. When the rhythm is synchronised with the day/night cycle, it is called as diurnal rhythm.

In humans, a circadian clock is located in the suprachismatic nuclei (SCN). The SCN is located in the hypothalamus. It is tiny cluster of about 10,000 nerve cells. This circadian clock is synchronised to the external cycles of light and darkness and social contact. Disruption of the clock or its synchronisation occurs during jet-lag, shift work and old-age. Disruption of the clock detrimentally affects our well being and mental and physical performance.

#### 5.6.2.1 Relevance of Biological Clock to Chemotherapy

One example of circadian rhythm is related to a hormone called melatonin. The pineal hormone, melatonin induces sleep and mediates seasonality. The SCN clock ensures that melatonin is secreted only at night. Melatonin secretion lasts longer on the longer winter nights. The duration of the circadian melatonin is used by the brain to orchestrate seasonal rhythms.

Melatonin is involved in circadian rhythm regulation, sleep, hormonal expression of darkness, seasonal reproduction, retinal physiology, antioxidant free-radical scavenging, cardiovascular regulation, immune activity, cancer control and lipid as well as glucose metabolism. It is also a member of an expanding group of regulatory factors which control cell proliferation and loss and is the only **chronobiotic hormonal regulator** of neoplastic cell growth.

At physiological concentrations, melatonin suppresses cell growth and multiplication and inhibits cancer cell proliferation in vitro through specific cell-cycle effects. At pharmacological concentrations, melatonin acts as a differentiating agent in some cancer cells and lowers their invasive and metastatic status by altering adhesion molecules and maintaining gap-junction intercellular communication. In other cancer cell types, melatonin, alone or with other agents, induces programmed cell death (apoptosis).

Biochemical and molecular mechanisms of melatonin's oncostatic action include regulation of estrogen receptor expression and transactivation, calcium/calmodulin activity, protein kinase C activity, cell structure and function, intracellular oxidation-reduction status, melatonin-receptor-mediated signal transduction cascades and fatty acid transport as well as metabolism. Thus melatonin has chronobiologically inhibitory regulation of cancer growth in maintaining host-cancer balance. This offers biological explanation of how melatonin enhances the efficacy and reduces the toxicity of chemotherapy and radiotherapy in cancer patients.

Several studies have demonstrated that progressive decline in pineal function is the most frequent endocrine alteration in cancer patients. A cytokine, IL-2 has anticancer activity. When tumours are resistant to IL-2 alone, combination with melatonin offers distinct clinical advantage. Melatonin along with cancer chemotherapy or radiotherapy reduces toxicity of chemotherapy/radiotherapy and enhances therapeutic efficacy. Melatonin is given orally once a day in the dark phase of the photoperiod at doses of 20-40 mg/day. It is observed that use of melatonin prolongs survival time of cancer patients.

Melatonin is successfully used in medical oncology alone or to biologically modulate conventional anticancer therapies, including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy. Clinical trials have shown that optimal timing of chemotherapy can lead to decreased toxicity and allow delivery of more dose intensive therapy.

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems which are sensitive modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electronic field, temperature, light and mechanical stimulation have been developed.

Chronotherapy has relevance to sleep, demensia, cardiovascular diseases, acute myocardial infarction, pulmonary embolism, asthma, arthritis.

Thus chronopharmacology offers new oppurtunities not only in cancer therapy but also for other diseases and technological development also.

## SUMMARY

**Principles of Toxicology**

**Acute, Subacute and Chronic Toxicity**

**Genotoxicity**

- Carcinogenicity
- Teratogenicity
- Metagenicity

**Principles of Treatment of Toxicity**

- Resuscitation and Stabilization
- Toxicological Diagnosis
- Therapeutic Interventions for Poisoning
- Supportive care
- Psychosocial and Workplace Safety Interventions

**Clinical Symptoms and Management of**

- Barbiturates
- Morphine
- Organophosphorous Compounds
- Lead Poisoning
- Mercury Poisoning
- Arsenic Poisoning

**Chronopharmacology**

- Definition of Rhythm and Cycles
- Biological Clock and its Significance
  - Relevance of Biological Clock to Chemotherapy

## REVIEW QUESTIONS

**Long Answer Questions**

1. Explain the term genotoxicity with suitable examples.
2. What is carcinogenicity? Classify carcinogens.
3. What is teratogenecity? Explain causes for it.
4. Define and classify mutagens with suitable examples.
5. Describe general principles for treatment of poisoning.
6. While noting history of poisoning, which factors should be addressed?
7. Which investigations are suggested for toxicological investigation?
8. Describe therapeutic interventions for poisoning.
9. Describe toxicokinetics, mechanism of toxicity for barbiturate poisoning.
10. Describe signs and symptoms of acute toxicity and clinical management of barbiturate toxicity.

11. What is mechanism of toxicity and toxicokinetic for morphine?
12. What are signs and symptoms of clinical toxicity and treatment of morphine poisoning?
13. Characterise the opioid withdrawal syndrome.
14. Describe mechanism of toxicity for organophosphates.
15. Describe signs and symptoms of acute toxicity and clinical management of OP poisoning.
16. Describe mechanism of toxicity and toxicokinetics of lead.
17. Describe signs and symptoms of acute and chronic toxicity and outline treatment of lead poisoning.
18. What is mechanism of toxicity and toxicokinetics of mercury salts.
19. What are signs and symptoms amd treatment of acute, sub-acute and chronic toxicity for mercury.
20. What is the mechanism of toxicity and toxicokinetics for arsenic?
21. What are signs and symptoms and treatment for acute and chronic toxicity for arsenic?
22. Describe role of melatonin in cancer therapy.

**Short Answer Questions**

1. Define following terms
   (a) Acute toxicity (b) Sub-acute toxicity
   (c) Chronic toxicity (d) Biological rhythm
2. What is Thalidomide tragedy?
3. What is the importance of resuscitation?
4. What is sympathomimetic toxindrome?
5. What is cholinergic toxindrome?
6. What is supportive care during poisoning?
7. What are psychosocial and safety interventions during poisoning?
8. Comment on tolerance and withdrawal symptoms for barbiturates.
9. Write short notes on
   (a) Naloxone (b) Naltrexone
   (c) Nalmefene (d) Addiction
   (e) Dependence (f) Tolerance
   (g) Carcinogenesis by arsenic
10. Name and characterise two organophosphate compounds.
11. Comment on occupational and environmental exposure for mercury.
12. Classify different types of rhythms.

# APPENDIX - I : ABBREVIATIONS

- **2-PAM:** 2-Pralidoxime
- **5-ASA:** 5-Amino Salycilic Acid
- **5-FC:** Flucytosine
- **5-FU:** 5-Fluracil
- **5-HT:** 5-Hydroxytryptamine
- **6-APA:** 6-Amino Penicillanic Acid
- **6-MP:** 6-Mercaptopurine
- **6-TG:** 6-Thioguanine
- **$A_1$:** Airway muscle (type)
- **ACh:** Acetylcholine
- **ACTH:** Adreno Cortico Tropic Hormone
- **ADH:** Antidiuretic hormone
- **AHG:** Antihaemophilic globulin
- **AIDS:** Acquired Immunodeficiency Syndrome
- **ALAD:** Aminolevulinic acid dehydratase (enzyme)
- **ALAS :** Aminolevulinic acid synthetase (enzyme)
- **APCs:** Antigen Presenting Cells
- **APSAC:** Anisoylated Plasminogen Streptokinase Activator Complex
- **ATG:** Anti Thymocyte Globulin
- **AZA:** Azathioprine
- **BAL:** British Anti-Lewisite (Dimercapol)
- **BBB:** Blood Brain Barrier
- **BCG:** Bacillus Calmette Guerin
- **BD:** Two Times a Day
- **BPCIA:** Biologics Price Competition and Innovation Act
- **cAMP:** Cyclic Adenosine Monophosphate
- **CCK:** Cholecystokinin
- **CCR5:** Chemokine Receptors 5
- **CD4+,$CD4^+$-T,CD8+:** Cluster of Differentiation (types of immune cells)
- **CDCA:** Cheno Deoxy Cholic Acid
- **CDKE:** Concentration-Depending Killing Effect
- **CDKs:** Cycline Dependent Kinases
- **CDSCO:** Central Drug Standardisation Control Organisation

- **CHF:** Congestive heart Failure
- **CIP:** CDK Inhibitory Proteins
- **CMC:** Carboxy-Methyl-Cellulose
- **CMV:** Cytomegalovirus
- **CNS:** Central Nervous System
- **COPD:** Chronic Obstructive Pulmonary Disease
- **CSF:** Cerebro Spinal Fluid
- **CSFs:** Colony Stimulating Fcators
- **CTZ:** Chemoreceptor Trigger Zone
- **CV:** Cardiovascular
- **CXCR4:** Chemokine coreceptor
- **CYP2C9, CYP2C19, CYP3A4:** Types of cytochrome emzymes
- **DMA:** Dimethyl Arsinic Acid
- **DMSA:** Dimercaptosuccinic acid
- **DOTS:** Directly Observed Therapy using Short course
- **dTMP:** Thymidine Mono Phosphate
- **EBB:** Epstein-Barr Virus
- **EBV:** Epstein-Barr Virus
- **ECL:** Enterochromaffin-like cell
- **EDTA:** Ethylene Diamine Tetraacetic acid
- **EGF:** Epidermal Growth Factor
- **EGFR:** Epidermal Growth Factor Receptor
- **EMA:** European Medicines Agency
- **EP:** Erythropoietin
- **ERA:** European Regulatory Agency
- **ETB:** Ethambutol
- **Fc ε $R_1$:** A type of receptor on mast cells and basophils
- **FDA:** Food and Drug Administration
- **$FEV_1$:** Forced Respiratory Volume in one second
- **FKBP-12:** FK-Binding Protein-12
- **FQs:** Fluoroquinolones
- **G6PD:** Glucose-6-Phosphate Dehydrogenase (enzyme)
- **GABA:** Gamma Amino Butyric Acid
- **GABAergic:** A neuron which generates GABA

- **GERD:** Gastro-Esophageal-Reflux -Disease
- **GIT:** Gastrointestinal tract
- **GMP:** Good Manufacturing Practices
- **cGMP:** Current Good Manufacturing Practices
- **Gn-RH:** Gonadotropin Releasing Hormone
- **gp41:** Glycoprotein 41 (antigen)
- **HAART:** Highly Active Anti –Retroviral Therapy
- **HBV:** Hepatitis B Virus
- **HDAC:** Histone deacetylase (enzyme)
- **HDN:** Haemolytic Disease of the Newborn
- **HIV:** Human Immunodeficiency Virus
- **HMM:** Hexamethylmelamine
- **HMG-CoA:** Hydroxy-Methyl-Glutaryl-Coenzyme A (enzyme)
- **HPV:** Human Papilloma Virus
- **HSV-1, HSV-2:** Herpes Simplex Virus type1, 2
- **HTLV I, HTLV II:** Human T cell Lymphotrophic Virus (types)
- **IARC:** International Agency for Research on Cancer
- **IDDM:** Insulin Dependent Diabetes Mellitus
- **IGF:** Insulin like Growth Factor
- **IgE:** Immunoglobulin E
- **IgF:** Immunoglobulin F
- **IgM:** Immunoglobulin M
- **IL:** Interleukin
- **IL-4, 5, 13:** Types of Interleukins
- **IM:** Imtramuscular
- **INF-α:** Interferon-alpha
- **INF-α2b:** Interferon-alpha2b
- **INF-β:** Interferon-beta
- **INF-Y:** Interferon-gamma
- **INH:** Isonicotinic hydrazide (Isoniazid)
- **iNOS:** Inducible nitric oxide synthase
- **INR:** International Normalised Ratio (Standardised Prothrombin Time)
- **IV:** Intravenous
- **$LC_0$:** Maximum Tolerable Concentration

- **$LC_{100}$:** Absolute Lethal Concentration
- **$LC_{50}$:** Median Lethal Concentration
- **$LC_{min}$:** Minimum Lethal Concentration
- **$LD_0$:** Maximum Tolerable Dose
- **$LD_{100}$:** Absolute Lethal Dose
- **$LD_{50}$:** Median Lethal Dose
- **LDL:** Low Density Lipoprotein
- **$LD_{min}$:** Minimum Lethal Dose
- **LFA-1:** Lymphocyte Functon-associated Antigen-1
- **LFT:** Liver Function Test
- **LOAEL:** Lowest Observed Adverse Effect Level
- **$LTC_4$, $LTD_4$, $LTE_4$:** Leukotrines of different types
- **$M_1$, $M_2$, $M_3$:** Muscarinic Receptors of different types for Acetylcholine
- **MAbs:** Monoclonal Antibodies
- **MAC:** Mycobacterium avium complex
- **MBC:** Minimum Bacterial Concentration
- **MDAC:** Multiple Dose Activated Charcoal
- **MDI:** Metered Dose Inhaler
- **MDR:** Multiple Drug Resistance
- **MIC:** Minimal Inhibitory Concentration
- **MMA:** Methylarsonic Acid
- **MPM:** Micophenolate Mofetil
- **m-RNA:** Messenger Ribonucleic acid
- **MRSA:** Methicillin-Resistant-Staphylococcus aureus
- **MSSA:** Methicillin-sensitive Staphylococcus aureus
- **MTC:** Maximum Tolerable Concentration
- **MTD:** Maximum Tolerable Dose
- **mTOR:** Mammalian Target of Rapamycin
- **MTX:** Methotrexate
- **NAcG:** N-Acetyl Glucosamine
- **NAcM:** N-Acetyl Muramic Acid
- **NANC:** Non-Adrenergic Non-Cholinergic
- **NBRA:** National Biotechnology Regulatory Authority
- **NFAT:** Nuclear Factor for Activated T cells

- **NK:** Natural killer (cells)
- **$N_N$:** Excitatory Cholinergic Nicotinic
- **NNRTIs:** Non Nucleoside Reverse Transcriptase Inhibitors
- **NO:** Nitric oxide
- **NOAEL:** No Observed Adverse Effect Level
- **NRTIs:** Nucleoside Reverse Transcriptase Inhibitors
- **NSAID:** Non Steroidal Anti-Inflammatory Drug
- **NtRTIs:** Nucleotide Reverse Transcriptase Inhibitors
- **OD:** Once Daily
- **OP:** Organophosphoruos/Organophosphate
- **OPIDN:** Organophosphate-Induced Delayed Neuropathy
- **ORS:** Oral Rehydration Salt
- **ORT:**Oral Rehydration Therapy
- **PABA:** Paraaminobenzoic acid
- **PAE:** Post Antibiotic Effect
- **PAF:** Platelet Activating Factor
- **PAH:** Para-Amino Hippuric Acid
- **PAS:** Para Amino Salicylic acid
- **PBP:** Penicillin Binding Protein
- **PD:** Pharmacodynamics
- **PDGF:** Platelet Derived Growth Factor
- **PEG:** Polyethylene Glycol
- **$PGD_2$, $PGE_2$, $PGI_2$:** Prostaglandin types: $D_2$, $E_2$, $I_2$
- **PID:** Pelvic Inflammatory Disease
- **PIs:** Protease Inhibitors
- **PK:** Pharmacokinetics
- **PMC:** Pseudo Membranous Colitis
- **PPI:** Proton Pump Inhibitor
- **PT:** Prothrombin Time
- **PTT:** Partial Thromboplastin Time
- **PVC:** Poly Vinyl Chloride
- **PZA:** Pyrazinamide
- **QID:** Four Times a Day
- **QS:** Quorum sensing
- **RA:** Rheumatoid Arthritis
- **Rh(D):** A type of antigen on the surface of RBCs

- **rIL:** Recombinant Interleukin
- **RMP:** Rifampicin
- **RNTCP:** Revised National Tuberculosis Control Programme
- **r-RNA:** Ribosomal Ribonucleic acid
- **RT:** Reverse transcriptase
- **rtPA:** Recombinant Tissue type Plasminogen Activator
- **SC:** Subcutaneous
- **SGOT:** Serum Glutamate Oxaloacetate Transaminase (enzyme)
- **SGPT:** Serum Glutamate Pyruvate Transaminase (enzyme)
- **-SH:** Sulphydryl
- **SIADH:** Syndrome of Inappropriate Antidiuretic Hormone
- **SLE:** Systemic Lupus Erythematosus
- **SM:** Streptomycin
- **STD:** Sexually Transmitted Disease
- **STEL:** Short Term Exposure Limit
- **TCR:** T cell Receptor
- **TDKE:** Time Dependent Killing Effect
- **TDS:** Three Times a Day
- **TGF-β:** Transforming Growth Factor Beta
- **THF:** Tetrahydrofolic acid
- **TID :** Three times a day
- **TLS:** Tumour Lysis Syndrome
- **TLV-C:** Threshold Limit Value-Ceiling
- **TLV-STEL:** Threshold Limit Value-Short Term Exposure Limit
- **TNF:** Tumour Necrosis Factor
- **TNF-α:** Tumour Necrosis Factor-alpha
- **t-RNA:** Transfer Ribo nucleic acid
- **UTI:** Urinary Tract Infection
- **VEGF:** Vascular Endothelial Growth Factor
- **VLDL:** Very Low Density Lipoprotein
- **VRSA:** Vancomycin Resistant Staphylococcus aureus
- **VZV:** Varicella Zoster Virus
- **WHO:** World Health Organisation
- **XDR:** Extensive Drug Resistant (tuberculosis)
- **ZES:** Zollinger Ellison Syndrome

# APPENDIX - II : EXPLANATIONS OF TERMS

- **Acetyl cholinesterase:** An enzyme which hydrolyses acetyl choline.
- **Achlorhydria:** A state where the production of hydrochloric acid in gastric secretions of the stomach and other digestive organs is absent or low.
- **Acidosis:** A process causing increased acidity in blood and other tissues.
- **Acrocyanosis:** A persistent blue or cyanotic discolouration of the extremities, most commonly in hand.
- **Acrodinia (pink disease):** A condition characterised by extreame irritability and restlessness.
- **Adsorbant:** Adhesion of substances on the surface of a solid.
- **Aerobic:** Requiring air, usually refers to oxygen.
- **Alcohol dehydrogenase:** A dehydrogenase enzyme which facilitates interconversion between alcohols and aldehydes.
- **Alkalosis:** A process reducing hydrogen ion concentration of arterial blood plasma.
- **Allograft rejection:** Rejection of tissue transplanted between two genetically different individuals of the same species.
- **Alopecia:** An autoimmune disorder resulting in unpredictable patchy hair loss.
- **Anaerobic :** Living in absence of free oxygen.
- **Analgesic:** Medicines used to relieve pain.
- **Anaphylaxis:** A severe, potentially life threatening allergic reaction.
- **Angioedema:** A rapid swelling of deep layers of skin.
- **Angioplasty:** Plastic repair of blood vessels.
- **Anorexia:** Decreased appetite.
- **Anti-emetic:** A drug which is effective against nausea and vomiting.
- **Antioncogenes:** A tumour suppressive gene.
- **Anti-tussives:** Agents that suppress cough.
- **Aphtous:** A condition characterised by repeated mouth ulcers.
- **Aplastic anaemia:** A disease in which body fails to produce blood cells in sufficient numbers.
- **Apoptosis:** Programmed cell death.
- **Arachnoiditis:** Inflammatory condition of arachnoid matter.
- **Arrhythmia:** A condition in which heart beat is irregular- too fast or too slow.
- **Arthralgia:** Joint pain.
- **Aspergillosis:** Disease caused by infection of fungi of the genus Aspergillus.
- **Astringent:** A chemical which shrinks or constricts body tissues.

- **Atopic dermatitis:** A type of inflammation of skin resulting in itchy, red, swollen and cracked skin.
- **Autoimmune:** A condition arising from an abnormal immune response to a normal body part.
- **Autonomic** (Nervous system)**:** A part of nervous system which acts unconsciously and regulates body functions like heart rate, respiratory rate, etc.
- **Bacteraemia:** Presence of bacteria in blood.
- **Bactericidal:** A substance that kills bacteria.
- **Bacteriostatic:** A substance that stops bacteria from reproducing.
- **Basal ganglia:** A group of sub-cortical nuclei in the brain.
- **Benign:** A tumour which lacks the ability to invade neighbouring tissue.
- **Bioavailability:** The degree and rate at which an administered drug is absorbed by the systemic circulation.
- **Biosimilars:** A biological product which is almost an identical copy of an original product.
- **Blastomycosis:** A fungal infection caused by inhaling Blastomyces dermatidis spores.
- **Bronchoconstriction:** Constriction of airways in the lungs.
- **Broncho-dilator:** A substance which dilates the bronchi and bronchioles.
- **Bronchorrhea:** Production of more than 100 ml/day of watery sputum.
- **Broncho-spasm:** A sudden constriction of muscles in the walls of bronchioles.
- **Brucellosis:** A contagious zoonosis caused by ingestion of unpasteurised milk or uncooked meat of infected animals.
- **Carcinogenicity:** Ability of a chemical to induce tumours.
- **Cardiotoxicity:** Occurrence of heart electrophysiology dysfunction or muscle damage.
- **Catecholamine:** A monoamine neurotransmitter related to sympathetic nervous system.
- **Cathartics:** A substance which accelerates defecation.
- **Chancroid:** A bacterial sexually transmitted infection with painful sores on the genetalia.
- **Chelation:** A type of bonding of ions and molecules to metal ions.
- **Chemoprophylaxis:** Administration of a medication for preventing a disease or infection.
- **Cholinergic:** A system composed of organised nerve cells which use acetyl choline for transmission.
- **Churg Strauss Syndrome:** Eosinophilic granulomatosis with poly angitis (EGPA); allergic granulomatosis.

- **Circadian rhythm:** A natural internal process which regulates the sleep-wake cycle and repeats every 24 hours.
- **Coccidioidomycosis (valley fever):** An infection caused by the fungus Coccidioides
- **Coma:** A deep state of prolonged unconsciousness.
- **Conjugation:** Transfer of genetic material between bacterial cells.
- **Conjunctivitis (pink eye):** An inflammation of outermost layer of white part of the eye.
- **Constipation:** Infrequent and frequently incomplete bowel movements.
- **Cor pulmonale:** A condition resulting out of complications from high blood pressure in pulmonary arteries.
- **Corpus striatum:** Is a nucleus (cluster of neurons) in the subcortical basal ganglia of brain.
- **Craving:** A psychological urge for the substance that is being with-held.
- **Cryptococcosis:** A potentially fatal fungal disease caused by the genus Cryptococcus.
- **Crystalluria:** Cloudy urine due to occurrence of crystals.
- **Cutaneous swelling:** Abnormal accumulation of fluid in the interstitium, located beneath the skin.
- **Cycloplegia:** Paralysis of the ciliary muscle of the eye, resuting in loss of accomodation.
- **Cystitis:** A urinary tract infection in lower urinary tract.
- **Cytokinesis:** The part of cell division process during which the cytoplasm of a single eukaryotic cell divides into two daughter cells.
- **Deciduous teeth:** First set of teeth in the growth development of humans.
- **Decongestant:** A drug used to relieve nasal congestion in the upper respiratory tract.
- **Demulsant:** An agent which forms a soothing film over mucus membrane.
- **Dendritic cells:** Antigen presenting cells of the mammalian immune system.
- **Dermatitis (eczema):** A group of diseases that result in inflammation of skin.
- **Dermatophytosis:** A fungal infection of the skin resulting in red itchy, scaly, circular rash.
- **Diaphoresis (perspiration/sweating):** Production of fluids secreted by sweat glands.
- **Diarrhoea:** A condition of having atleast three loose, liquid, or watery bowel movements each day.
- **Dihydrofolate reductase(DHFR):** An enzyme which reduces dihydrofolic acid to tetrahydrofolic acid.
- **Disulfiram:** A drug used to support the treatment of chronic alcoholism by producing an acute sensitivity to ethanol.

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- **Disulfiram like drug:** A drug which causes adverse reactions to alcohol leading to nausea, vomiting, flushing, dizziness, throbbing headache, tachycardia and hypotension.
- **Diurnal:** Any pattern that reccurs daily.
- **Dizziness:** An impairment in spatial perception and stability.
- **Domiciliary care:** A care provided to people in their own homes.
- **Dysarthria:** A motor speech disorder in which spoken words are broken.
- **Dyspepsia:** A condition of impaired digestion resulting in abdominal fullness.
- **Dyspnoea:** Shortness of breath.
- **Dysrrhythmia:** Disturbance of rhythm of heart.
- **Dystonia:** A neurological movement disorder resulting in twisting and repeatitive movements.
- **Dysuria:** Painful urination.
- **Efflux:** A mechanism responsible for moving compounds out of cells.
- **Emesis:** Vomiting.
- **Emetic:** An agent which causes vomiting.
- **Emphysema:** A set of diseases where flow of air in the lungs is obstructed.
- **Enkephalin:** A pentapeptide involved in regulating nociception in the body.
- **Encephalopathy:** A disorder of the brain with chronic degenerative changes.
- **Endocarditis:** Inflammation of inner layer of heart, endocardium.
- **Entero-hepatic circulation:** Circulation of biliary acids, bilirubin, drugs or other substances from the liver to the bile and back to liver through intestine.
- **Enterotoxin:** A protein exotoxin released by a microorganism that targets the intestines.
- **Enzyme inducer:** A drug which increases the metabolic activity of an enzyme.
- **Eosinophilia:** A condition in which eosinophil count in blood exceeds $5.0 \times 10^8$/L.
- **Epigastric distress:** A pain in epigastric region.
- **Episodic:** Related to specific incidence.
- **Erythema:** Redness of skin or mucus membrane.
- **Erythrocytic:** Within red blood cells.
- **Eukaryotic:** Related to organisms whose cells have a nucleus enclosed within membrane.
- **Exacerbation:** Worsening of a disease or an increase in its symptoms.
- **Exo-erythrocytic:** Outside red blood cells.
- **Extra-pyramidal side effects:** Physical symptoms including tremor, slurred speech, akathesia, anxiety, etc associated with antipsychotic drugs.
- **Extrinsic:** A property which is not essential or inherent to the subject.

- **Fanconi's syndrome:** A syndrome of inadequate reabsorption in the proximal renal tubules of the kidney.
- **Fibroma:** A benign sex cord-stromal tumour.
- **Flu-like syndrome:** Symptoms involving sore throat, fever, headache, muscle aches, congestion and cough.
- **Flushing:** Feeling of warmth and rapid reddening of neck, upper chest or face.
- **Fungicidal:** A chemical or biological organism used to kill parasitc fungi or their spores.
- **Fungistatic:** An antifungal agent which inhibit the growth of fungus without killing them.
- **Galactorrhoea:** Spontaneous flow of milk from the breast.
- **Gametocyte:** The sexual plasmodial cell in malarial blood which produces gametes in the insect host.
- **Ganglion:** A mass of grey substance in the nervous system, specially an aggregation of cell bodies of neurons outside the CNS.
- **Gastric lavage:** Washing out or irrigation of stomach contents.
- **Gastroenteritis:** Inflammation of stomach and intestines.
- **Genotoxicity:** Property of chemical agents that damages the genetic information within a cell.
- **Gingival hyperplasia:** Overgrowth of gum tissue around the teeth.
- **Globus pallidus:** A structure in the brain, a part of basal ganglia involved in regulation of voluntary movement.
- **Glutathione:** An antioxidant produced in the cells.
- **Glycosylation:** The reaction in which a carbohydrate is attached to a hydroxyl or other functional group of another molecule.
- **Gonorrhoea:** A sexually transmitted disease cuasing serious and permanent health problems in both men and women.
- **Granuloma inguinale:** A chronic bacterial infection associated with sexually transmitted diseases.
- **Granulomatous:** A collection of immune cells, macrophages, involved in inflammation.
- **Gray baby syndrome:** A rare and serious side effect in new born infants following accumulation of Chloramphenicol.
- **Gynaecomastia:** Increase in the amount of breast gland tissue in men.
- **Habituation:** A form of non-associative learning process where there is decrease in response to a stimulus after being repeatedly exposed to it.
- **Haematuria :** Appearance of blood in urine.
- **Haemodialysis:** A dialysis machine with a special filter used to clean blood.

- **Haemoperfusion:** A method of filtering blood to remove a toxin.
- **Haemophilia:** A genetic disorder in which blood does not clot normally.
- **Haemopoietic:** Pertaining to the formation of blood or blood cells.
- **Half-life:** Time taken to reduce concentration of a drug in blood to its half.
- **Hallucinations:** An experience in which you see, hear, feel or smell something which does not exist.
- **Hepatitis:** Inflammatory condition of liver.
- **Hepatotoxicity:** Chemical-driven liver damage.
- **Herbicide:** Substances used to control unwanted plants (weeds).
- **Hippocampus:** A major component of brain embedded deep in temporal lobe of cerebral cortex which regulates motivation, emotion, learning and memory.
- **Hirsutism:** A coarse or coloured hair which grows on the face and body of some women.
- **Histoplasmosis:** An infection caused by the fungus called Histoplasma.
- **Hodgkin's lymphoma:** A type of lymphoma in which cancer originates from lymphocytes.
- **Homeostasis:** A state of steady internal physical and chemical conditions maintained by living systems.
- **Hospital acquired infections:** An infection originating from a hospital; usually they are resistant to antibiotics.
- **Hydatid disease:** A disease caused by infection with a small tapeworm parasite.
- **Hyperaemia:** Excess of blood in a part of body.
- **Hyperbilirubinaemia:** Excess of bilirubin in blood.
- **Hypercapnia:** Abnormally elevated levels of carbon dioxide in blood.
- **Hyperkeratosis:** Thickening of outer layer of skin.
- **Hyperlipidaemia:** Higher levels of lipids, including cholesterol in blood.
- **Hypermagnesaemia:** Higher levels of magnesium in blood.
- **Hypermotility:** Abnormal or excessive movement of GIT.
- **Hyperosmolarity:** A condition of body fluids where osmotic pressure is higher than that of body fluids.
- **Hyperphosphataemia:** Abnormally high levels of serum phosphates.
- **Hyperpyrexia:** High fever.
- **Hypersensitivity:** Undesirable reactions produced by normal immune system including allergies.
- **Hyperuricaemia:** Higher levels of uric acid in blood.
- **Hypnozoites:** The latent stages of malarial parasite.
- **Hypochlorhydria:** Low level of stomach in acid.

- **Hypochromic:** A kind of anaemia in which RBCs are pale.
- **Hypocoagulability:** Structural or functional abnormalities in blood resulting in decreased coagulation, causing bleeding.
- **Hypofibrinogenaemia:** Abnormal deficiency of fibrinogenin blood.
- **Hypophosphataemia:** A rare, fatal metabolic bone disease ue to lower levels of phosphates in blood.
- **Hypothermia:** Decrease of body temperature below normal level.
- **Hypoxaemia:** Abnormally low level of oxygen in blood.
- **Idiosyncratic:** Peculiar individual reactions (to drugs).
- **Immunocompromised:** Reduced level of immunity.
- **Immunomodulator:** An agent which modulates immunological defense.
- **Immunostimulant:** An agent which stimulates immunity.
- **Immunosuppressive:** An agent which reduces immunity.
- **Inflammatory bowel disease(IBD):** Disorder which involves chronic inflammation of digestive tract.
- **Infradian (rhythm):** A rhythm with a period longer than a day.
- **Insecticide:** A substance used to kill insects.
- **Insomnia:** Asleep disorder characterized by difficulty in staying asleep.
- **Integrase:** A viral enzyme which catalyzes integration of virally derived DNA into the host cell DNA.
- **Integron:** A mobile DNA element that can capture and carry genes responsible for antibiotic resistance.
- **Intestinal fibrosis:** A potentially serious complication of IBD causing fibrotic strictures.
- **Intraocular pressure:** The pressure of fluid inside the eye.
- **Intrinsic:** Due to causes of factors within a body or organ.
- **Ionotropy :** Related to force or energy of heart's muscular contraction.
- **Jarish-Herxheimer reaction:** A reaction to endotoxin-like products released by the death of harmful microbes within the body during antibiotic treatment.
- **Kala azar:** A chronic and potentially fatal disease of the viscera due to *Leishmania donovani.*
- **Kaposi's sarcoma:** A type of cancer that forms masses in the skin, lymph nodes or other organs.
- **Keratin:** A fibrous structural protein making up hair, nails and outer layers of skin.
- **Kernicterus :** Preventable brain damage in newborns with jaundice.
- **Lachrymation :** The flow of tears from eyes.
- **Laxative:** A substance which loosen stools and increase the bowel movements.

- **Lead-line:** A clinical sign found in patients with chronic lead poisoning. It is a thin black-blue line visible along the margin of gums.
- **Legionnaire's pneumonia:** A typical pneumonia caused by Legionella bacteria.
- **Leishmaniasis :**A vectorborne disease transmitted by sandflies associated with skin ulcers,fever, anaemia.
- **Leukaemia:**A cancer of blood or bone marrow causing sweat, fatigue and fever.
- **Leukocytosis:** An incease in number of WBCs due to infection.
- **Limbic system:** Subcortical structures in the brain involved in motivation, emotion, learning and memory.
- **Lymphadenopathy:** A disease of lymph nodes.
- **Lymphatic filariasis:** A parasitic disease caused by thread-like worms which live in human lymph systems.
- **Lymphogranuloma venereum:** A chronic infection of lymphatic system caused by 3 different types of bacteria.
- **Lymphoma:** A cancer of lymphocytes.
- **Macrophages:** Types of phagocytes responsible for detecting, engulfing and destroying pathogens and apoptoic cells.
- **Malaise:** A general feeling of discomfort, illness or unease whose exact cause is difficult to know.
- **Malignant:**Type of cells related to cancer.
- **Meningitis:** Inflammation of meninges, membranes covering the brain and spinal cord.
- **Mesna :** A drug used to reduce side effects of certain chemotherapeutic drugs.
- **Metastasis:** The development of secondary malignant growths at a distance from primary site of cancer.
- **Methyl xanthines:** A class of drugs derived from the purine base, Xanthine.
- **Micturition:** Sense of urination.
- **Mitosis:** A process where a single cell divides into two identical daughter cells.
- **Mucociliary:** Movement of mucous due to cilia in airways.
- **Mucokinetic:** Clearance of mucous from upper and lower airways.
- **Mucolytic :** A drug which thins mucous.
- **Mucormycosis :** A fungal infection caused by fungi in the order Mucorates.
- **Multibacillary (lepromatous) leprosy:** A type of leprosy in which patients show a wide spectrum of clinical manifestations.
- **Multiple sclerosis :**A potentially disabling disease of the brain, spinal cord disrupting flow of information and damaging insulating cover of nerve cells.
- **Murine :** Relating to mice or related rodents.

- **Mutagen:** An agent which damages the genetic material,usually DNA.
- **Mutagenicity :** Ability to damage the genetic material, usually DNA.
- **Myalgia:** Muscle pain.
- **Myasthenia gravis:** A disease characterized by weakness and rapid fatigue of muscles.
- **Mycosis :** A fungal infection of animals and humans.
- **Mydriasis:** Dilatation of pupil.
- **Myelosuppression:** A condition in which bone marrow activity is decreased.
- **Myoma:** Benign tumours that grow from muscles.
- **Myopathy:** A disease of muscles in which the muscle fibres do not function properly.
- **Myosis:** Constricion of the pupil of eye.
- **Myositis:** Inflammation of the muscles.
- **Narcotic:** A substance used to treat moderate to severe pain.
- **Neoplasm:** An abnormal mass of tissue that results when cells divide more than they should or do not die when they should.
- **Nephrotic syndrome :** A kidney disese with proteinuria, hypoalbuminemia and edema.
- **Nephrotoxic :** A substance which is toxic to the kidneys.
- **Nephrotoxicity:** Toxicity in the kidneys.
- **Neuraminidase:** An enzyme which cleaves glycosidic linkages of neuraminic acid.
- **Neuritis:** Inflammation of nerves.
- **Neurofibroma :** A noncancerous nerve tumour that can appear anywhere in the body.
- **Neuromuscular blockade:** A condition in which transmission between neve and muscle is blocked.
- **Neuropathy :** A result of damage of nerves.
- **Neurosyphilis:** Infection of CNS in patients of Syphilis.
- **Neutropenia;** Abnormally low concentration of neutrophils in the blood.
- **Nitric oxide synthase:** An enzyme involved in synthesis of nitric oxide.
- **Normocapnic :** Having normal amount of carbon dioxide in arterial blood.
- **Normocytic :** A state where RBCs are normal in size and in haemoglobin content.
- **Oedema:** A state with fluid retention in body causing swelling in feet and ankles.
- **Oesophagitis:** A disese characterized by inflammation of the oesophagous.
- **Oilgonucleotide:** Short DNA or RNA molecules, oligomers used in research, genetic testing and forensics.
- **Oliguria:** A condition in which urine output is less than 400 ml in adults.
- **Oncogenes :** Genes that have a potential to cause cancer.

- **Opioid:** A drug related to Morhine/Heroin.
- **Opsonisation :** A process by which the pathogen is marked for ingestion and elimination by the phagocytes.
- **Optic atrophy;** Degeneration of, or damage to the optic neve supplying to eye.
- **Optic neuritis :** Inflammation of the optic nerve.
- **Oropharyngeal :** A part of at the back of mouth behind oral cavity.
- **Osteomyelitis:** An infection in the bone.
- **Osteoporosis:** A bone disease in which body looses too much bone and makes it brittle.
- **Ototoxicity :** Being toxic to ear, specially cochlea or auditory nerve.
- **Oxidative phosphorylation:** The metabolic pathway in which cells use enzymes to oxidize nutrients and generate ATP.
- **Pancreatitis:** Inflammation of the pancreas.
- **Paresis :** A condition characterized by weaknes of voluntary movements.
- **Paresthesia:** An abnormal dermal sensation with no apparent physical cause.
- **Parkinson's disease:** A progressive nervous system disorder that affects movement.
- **Paronychia:** A skin infection around the fingernails and toenail.
- **Paucibacillary (tuberculoid) leprosy:** Leprosy patients which show negative smears at all sites are grouped as Paucibacillary type.
- **Peptic ulcer:** Sores which develop on the inside lining of stomach or duodenum.
- **Peristalisis:** Radially symmetrical contraction and relaxation of muscles which propagates in GIT.
- **Phlebitis:** Inflammation of a vein.
- **Phosphodiesterase:** An enzyme which breaks phosphodiester bond.
- **Photophobia :** The process of avoiding light.
- **Photosensitivity :** An extreme sensititvity to UV rays from the Sun or other sources.
- **Phototoxicity :** Toxic effects of light.
- **Physical dependence:** A physical condition caused by chronic use of a tolerance-forming drug.
- **Piloerection:** Erection of hairs due to involuntary contraction of muscles at the base of hair.
- **Pneumonitis:** Inflammation of the lung.
- **Polyoma virus nephropathy:** Damge to the nerve caused by Polyoma virus.
- **Polyuria:** Frequent urination.
- **Porphyria :** Appearnce of porphyrin in urine.

- **Postsynaptic:** Next to synapse, a part at the end of nerve.
- **Pre-erythrocytic:** A stage before entering in RBCs
- **Presynaptic :** Earlier to synapse, a tart at the end of nerve.
- **Probiotics :** Live bacteria and yeasts which are good for digestive system.
- **Pro-drug:** A medication/compound, which is metabolized to a pharmacologically active drug.
- **Prokaryotic:** Unicellular organisms which lack internal membrane-bound structures.
- **Prosthetic valve:** A valve used for replacement in the heart for functional properties.
- **Proteinuria:** Appearance of protein in urine.
- **Pruritus:** Itchy skin worsened by dry skin.
- **Pseudolithiasis:** Unusual complication where the drug complexes with Calcium and mimicks gallstones.
- **Pseudomembranous colitis:** Inflammation of colon due to overgrowth of *Clostridium difficile.*
- **Psoriasis:** A common skin condition that speeds up the life cycle of skin cells.
- **Psychological dependence:** A state that involves emotional-motivational withdrawal symptoms on cessation of a drug.
- **Puerperium:** The time from delivery of the placenta through the first few weeks of delivery.
- **Pulmonary oedema:** A condition caused by excess fluid in the lungs.
- **Purgative:** An agent which causes purging or cleansing by evacuation of bowels.
- **Pyelonephritis:** A sudden and severe kidney infection.
- **Pyrogenic :**Producing heat in the body.
- **QTc prolongation:** A surrogate marker of the risk of arrhythmia by prolonging QT interval in the record of ECG.
- **Raynaud's phenonmenon:** A type of vascular disease characterized by a pale to blue to red colour at extremities due to reduced blood flow.
- **Renal toxicity (Nephrotoxicity):** Toxic effects on the kidney.
- **Resuscitation:** The process of correcting physiological disorders in an acutely ill patient.
- **Retinitis:** Infflamation of retina of the eye.
- **Retinopathy:** Damage to retina of the eye.
- **Retrovirus:** A virus that is composed not of DNA but of RNA.
- **Reverse transcriptase:**An enzyme used to generate complimentary DNA (c DNA) from an RNA template.

- **Rhabdomyolysis:** A serious syndrome due to direct or indirect muscle injury leading to muscle pain, weakness and vomiting.
- **Rheumatoid arthritis:** A chronic inflammatory disorder causing inflammation in two or more joints.
- **Rhinitis:** An irritation and inflammation of mucous membrane inside the nose.
- **R-plasmids:** Resistance plasmids containing genes which provide resistance against antibiotics or poisons.
- **Sarcoma:** A rare kind of cancer that grows in connective tissues.
- **Schizogony :** Asexual reproduction by multiple fission, found in some protozoa, especially parasitic sprozoans (of malaria parasite).
- **Schizont:** A cell that divides by schizogony to form daughter cells.
- **Schizonticide:** An agent selectively destructive of the schizont of a sporozoan parasite.
- **Seborrheic dermatitis:** A common skin condition that mainly affects scalp. It causes redness, scaly patches, dandruff, ithy rashes and white scales.
- **Septicaemia:** A serious bloodstream infection.
- **Serum sickness:** A type of hypersensitivity reaction that results from the injection of foreign protein or serum.
- **Sialylation:** A process by which sialic acid groups are introduced onto molecules.
- **Sneezing:** Powerful expulsion of air that removes irritants from nose or throat.
- **Somatic :** Cells of the body other than germ cells.
- **Sporontocides:** Any substance that kills sporonts.
- **Sporotrichosis:** A rare infection caused by a fungus called sporothrix.
- **St . John's wort:** A flowering plant , *Hypericum perforatum.*
- **Status asthmaticus:** A medical emergency, an extreme form of asthma which can lead to hypoxemia.
- **Steroidogenesis :** Synthesis of steroids in the body.
- **Stevens Johnson syndrome:** A rare serious disorder of skin and mucous membranes causing epidermal nacrolysis.
- **Stupor:** A state of near-unconsciousness or insesibility.
- **Superinfection:** A second infection superimposed on earlier one as a result of antimicrobial therapy.
- **Superoxide:** A compound that contains superoxide ion, which is anionic form of $O_2$.
- **Sympathomimetics:** Stimulant compounds which mimick the effects of noradrenalin/adrenaline.

- **Synapse:** A structure in the nervous system that permits a neuron to pass an electrical or chemical signal to another neuron.
- **Synergistic :** Various components work together to produce enhanced results.
- **Syphilis:** A highly contagious disease spread by sexual activity.
- **Systemic lupus erythematosus:** A chronic disease which causes inflammation in connective tissues.
- **Tachypnoea:** A respiratory condition result in in fast and shallow breathing.
- **Tendonitis:** Inflammation or irritation of a tendon.
- **Teratogenecity:** A manifestation of developmental toxicity, representing a particular case of embrotoxicity.
- **Thrombocytopenia:** A condition leading to low platelet count.
- **Thrombophlebitis:** An inflammatory process that causes a blood clot to form and block one or more veins:
- **Tinnitus:** The perception of noise or ringing in the ears.
- **Tolerance:** A state when the person no longer responds to the drug in the way that was initially responded; usually it is a diminished response.
- **Topical:** Applied to a particular place on or in the body.
- **Topoisomerase:** An enzyme that participates in the overwinding or underwinding of DNA.
- **Toxindrome :** A set of toxicity symptoms which is characteristic of a type of poison.
- **Transduction:** A process by which foreign DNA is introduced into a cell by a virus or viral vector.
- **Transformation :** A genetic alteration of a cell resulting from the direct uptake and incorporation of exogenous genetic material.
- **Translocation :** A chromosome abnormality caused by exchange of parts between non-homologous chromosomes.
- **Transpeptidation:** The process of transferring an amino acid or a group of amino acids from one compound to another.
- **Transposon:** Class of genetic elements that can jump to different locations within a genome.
- **Traveller's diarrhoea:** A stomach or intestinal infection associated with travel.
- **Ultradian:** A cycle repeated every 24 hours.
- **Urethritis:** A condition in which urethra becomes inflamed or irritated.
- **Urinary incontinence:** The loss of urinary bladder control leading to uncontrolled urination.
- **Urticaria:** An outbreak of swollen, pale red bumps or wheals on the skin.

- **Uveitis:** A form of eye inflammation.
- **Vaginitis :** An inflammation of the vagina.
- **Vasospasm:** Contraction of a vein as a protective mechanism.
- **Vector:** An organism that does not cause a disease itself but spreads infection by conveying pathogens from one host to another.
- **Veneral warts:** Warts related to veneral diseases.
- **Vomitus:** Matter from the stomach which has come up and ejected beyond the mouth.
- **Warts :** Raised bumps on the skin.
- **Wegener's granulomatosis:** A rare multisystem autoimmune disease related to blood vessel disorders.
- **Wheezing:** A high- pitched whistling sound during breathing.
- **Whooping cough:** A bacterial infection that causes un controllable violent coughing, also known as pertussis.
- **Xerostomia:** Dry mouth resulting from reduced saliva.
- **Zollinger Ellison syndrome:** A rare condition in which tumors cause the stomach to produce excessive acid.

# OUR UPCOMING BOOKS

## As Per PCI Regulations Third Year (Semester VI)

- **Medicinal Chemistry III :** S.G. Walode
- **Medicinal Chemistry III :** K.G. Bothara
- **Practical Medicinal chemistry III :** S.G. Walode
- **Pharmacology III :** Dr. S. V. Tembhurne
- **Pharmacology III :** K.G. Bothara, K.K. Bothara
- **Practical Pharmacology III :** Dr. Arjun Patra
- **Herbal Drug Technology :** Vaibhav shinde, Ms. K. S. Bodas, S.B. Gokhale
- **Practical Herbal Drug Technology :** Vaibhav Shinde, Ms. K. S. Bodas, S.B. Gokhale
- **Biopharmaceutics and Pharmacokinetics :** Sunil bakliwal
- **Pharmaceutical Biotechnology :** Dr. Chandrakant Kokare
- **Medicinal Chemistry III :** Dr. Abhishek Tiwari
- **Pharmacology III :** Dr. Rupesh Gautam, Dr. Kalpesh Gour
- **Herbal Drug Technology :** Dr. Versha Tiwari, Dr. Vikash Sharma
- **Biopharmaceutics and Pharmacokinetics :** Hari Kumar
- **Pharmaceutical Biotechnology :** Dr. Khush Yadav, Mr. Rajiv Saxena, Ms. Satinder Kaur, Garima Joshi
- **Quality Assurance :** Bhupender Sing Tomar, Dr. Pawan Jhalwal, Surajpal verma
- **Medicinal Chemistry III :** Vibha Chandan Patil, Dr Chandrashekhar Narajji
- **Medicinal Chemistry III :** Mr. Mayur S. Jain, Mr. Mayur R. Bhurat, Sanjay A. Nagdev, Dr. Md. Rageeb Md. Usman
- **Practical Medicinal Chemistry III :** Dr. Sunita T. Patil, Dr. Md. Rageeb Md. Usman, Dr. Parloop A. Bhatt
- **Pharmacology III :** Dr. Manjunatha. P. Mudagal
- **Practical Pharmacology III :** Dr. Manjunatha. P. Mudagal
- **Herbal Drug Technology :** Kuntal Das
- **Herbal Drug Technology :** Dr. Santram Lodhi, Dr. Md. Rageeb Md. Usman, Dr. Tushar A. Deshmukh, Mr. Vaibhav M. Darvhekar
- **Practical Herbal Drug Technology :** Prof. Md. Rageeb Md. Usman, Prof. Vaibhav M. Darvhekar, Prof. (Dr.) Akhila S., Prof. (Dr.) Vijay Kumar D.
- **Biopharmaceutics and Pharmacokinetics :** Dr. B. Prakash Rao
- **Pharmaceutical Biotechnology :** Kuntal Das
- **A Practical Book Of Medicinal Chemistry (Combined Book Sem. IV & VI)** Dr. Abhishek Tiwari, Dr. Rajeev Kumar

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