Vitamin K

- Vitamin K, a fat-soluble vitamin, is required for the synthesis of clotting factors. It exists in different forms:
  - **Vitamin K1 (phytonadione)** is from plant and animal source;
  - **vitamin K2 (menaquinone)** is produced by intestinal bacteria and is stored in hepatic tissue,
  - **vitamin K3 (menadione)** is a synthetic form.

- All three forms of vitamin K (K1, K2 and K3) are naphthoquinone derivatives.

Dietary source:
Vitamin K is found in spinach, cabbage, cauliflower and tomatoes. It is also present in butter, meat, milk, liver. The average daily intake for an adult is estimated to be 70–140 mcg/day.

Pharmacokinetics:
- Vitamin K1 and K2 require the presence of bile for their absorption while watersoluble forms can be absorbed in the absence of bile.
- Vitamin K is transported along with low-density lipoprotein (LDL) and is stored mainly in the liver.
- It is metabolized by glucuronide and sulphate conjugation and metabolites are excreted in bile and urine.

Actions:
Vitamin K acts as a cofactor for carboxylation of glutamic acid residues of clotting factors (II, VII, IX and X).

Deficiency:
- Vitamin K deficiency may occur due to inadequate absorption (lack of bile salts)
- Loss of vitamin (chronic diarrhoea) and administration of broad-spectrum antibiotics (suppression of bacterial flora).
In vitamin K deficiency, there is an increased tendency to bleed—epistaxis, haematuria, gastrointestinal bleeding and post-operative bleeding.

**Preparations**

- **Phytonadione (vitamin K1):** It is available for oral, subcutaneous (s.c.), intramuscular (i.m.) and intravenous (i.v.) administration.
- **Menadiol sodium diphosphate (vitamin K3):** It is a water-soluble preparation and is available for i.v., i.m. and oral administration.

**Uses**

1. For **prevention and treatment of bleeding** associated with vitamin K deficiency.

2. In **obstructive jaundice** with haemorrhagic symptoms, parenteral vitamin K1 is preferred.

3. **Vitamin K1 (1 mg phytonadione, i.m.)** is given routinely to all neonates to prevent bleeding, as the intestinal flora—which is necessary for the synthesis of vitamin K—is not developed.

4. To **control bleeding due to oral anticoagulant therapy,** phytonadione is used.

5. Vitamin K1 is used in **salicylate poisoning with haemorrhagic complications.**

**Adverse effects**

**Oral vitamin K is safe.**

- Intravenous injection may cause flushing, sweating, dyspnoea, hypotension, cyanosis, collapse and **anaphylactic reaction.**
- Administration of vitamin K through intramuscular and s.c. routes may cause **severe pain.**
- **Menadione may cause haemolysis, hyperbilirubinaemia and kernicterus in newborn, hence is not used.**
Fibrinogen
- It is obtained from human plasma.
- It is used to control bleeding associated with hypofibrinogenaemia and is infused intravenously.

Antihaeomophilic factor
- It contains coagulation factor VIII with von Willebrand’s factor.
- It is used to control bleeding episodes in haemophiliacs.
- It is administered as i.v. infusion.
- Adverse effects include fever with chills, headache and skin rashes.

Ethamsylate
- It is a haemostatic, available for oral, i.m. and i.v. administration.
- It corrects abnormal platelet adhesion and also maintains the stability of the capillary wall.
- It is well absorbed after oral administration, secreted in breast milk and excreted unchanged in urine.
- It is used for prophylaxis and to control bleeding from small blood vessels e.g. following tooth extraction, epistaxis, etc.
- It may cause skin rashes, hypotension and headache.
Anticoagulants

- Anticoagulants are drugs that prevent or reduce coagulability of blood.

Classification

1. Used in vitro:
   - Heparin
   - Sodium citrate Used in blood banks to store blood.
   - Sodium oxalate
   - Sodium edetate Used as an anticoagulant in laboratory

2. Used in vivo:
   Parenteral anticoagulants
   - Heparin [unfractionated heparin (UFH)].
   - Low-molecular-weight heparins (LMWHs): Enoxaparin, dalteparin, tinzaparin, ardeparin, reviparin.
   - Synthetic - Fondaparinux.
   - Direct thrombin inhibitors: Lepirudin, bivalirudin.

Oral anticoagulants
   - Coumarin derivatives- Warfarin, dicumarol.
   - Indandione derivatives- Phenindione.
   - Oral direct thrombin inhibitor-Dabigatran etexilate.

Parenteral Anticoagulants

Heparin (Unfractionated Heparin [UFH])
   - Heparin was discovered by a medical student, McLean. It was later isolated identified by Howell as a sulphated mucopolysaccharide.
   - Because of its high concentration in liver, it was named heparin.
   - A strong electronegative compound, it is the strongest organic acid in the body.
   - Commercially, heparin is obtained from ox lung and pig intestinal mucosa.

Mechanism of action
Heparin is an indirect thrombin inhibitor.
   - Heparin binds and accelerates the activity of plasma antithrombin III.
- Heparin antithrombin III complex then inhibits activated clotting factors Xa, IIa, IXa, XIa, XIIa and XIIIa by forming stable complexes with them.

- At low concentration, heparin selectively inhibits the conversion of prothrombin to thrombin.

- Heparin thus prevents further thrombus formation.

- Heparin in high doses has antiplatelet action and, thereby, prolongs the bleeding time.

- Heparin reduces the blood lipid level by releasing lipoprotein lipase from vessel wall and tissues.

**Pharmacokinetics**

- Heparin is not absorbed after oral administration because of its high negative charge and large molecular size.
- Therefore, it must be given parenterally—intravenously or subcutaneously.
- On i.v. administration, the anticoagulant effect starts immediately,
Through s.c. route, it takes 1–2 hours.
Heparin is highly protein bound.
It does not cross the blood–brain barrier or placental barrier and is safe during pregnancy.
It is rapidly inactivated in the liver by heparinase and the metabolites are excreted in urine.

Mode of administration
- Heparin is administered by i.v. infusion and i.v. intermittent injection (for treatment) or
- s.c. route (for prophylaxis).

Administration of heparin intramuscularly may cause haematomas; hence, this route should not be used.
- During heparin therapy, activated partial thromboplastin time (aPTT) monitoring is necessary.

Adverse effects and contraindications
1. Bleeding:
   - Bleeding can occur in the urinary and gastrointestinal tract or anywhere in the body.
   - It can be controlled rapidly by slow i.v. infusion of protamine sulphate (heparin antagonist).
   - It is a strongly basic protein and hence rapidly neutralizes the anticoagulant effect of heparin.
   - It is obtained from fish sperm.
   - One milligram of protamine sulphate approximately neutralizes 100 units of heparin (chemical antagonism).

2. Heparin-induced thrombocytopenia (HIT)
3. Hypersensitivity. They are skin rashes, urticaria, fever, etc.
4. Osteoporosis
5. Reversible alopecia has been reported.
   Heparin is contraindicated in haemophiliacs, patients with heparin-induced thrombocytopenia (HIT), severe hypertension, intracranial haemorrhage, bacterial endocarditis, active tuberculosis, peptic ulcer, threatened abortion, cirrhosis, renal failure, etc.
Low-molecular-weight heparins (LMWHs)
- Enoxaparin, dalteparin, tinzaparin, ardeparin, reviparin, etc. are LMWHs and are isolated from standard heparin by various techniques.
- LMWHs are indirect thrombin inhibitors—produce anticoagulant effect mainly by inhibition of factor Xa through antithrombin.

Low-molecular-weight heparins are given subcutaneously.

The following are the advantages of LMWHs
1. They have a higher s.c. bioavailability as compared to UFH.
2. They have a longer duration of action.
3. They do not routinely require aPTT monitoring.
4. There is a lower incidence of thrombocytopaenia and osteoporosis.
(Uses, adverse effects and contraindications are same as other anticoagulants)

Fondaparinux
- It is a synthetic parenteral anticoagulant.
- It binds to antithrombin and selectively inhibits factor Xa (indirect thrombin inhibitor).
- It does not require routine laboratory monitoring.
- Fondaparinux is administered subcutaneously.
- It is useful in pulmonary embolism and deep vein thrombosis (DVT).
- Incidence of thrombocytopaenia is lower with fondaparinux.

Direct thrombin inhibitors
- Lepirudin and bivalirudin combine directly and inactivate thrombin without binding to antithrombin III.
- They are used in patients who are at risk of heparin induced thrombocytopaenia.
Oral Anticoagulants

Among oral anticoagulants, coumarin derivatives are commonly used. Oral anticoagulants act only in vivo. They are vitamin K antagonists.

Mechanism of action (Fig. 9.2)

- Clotting factors II, VII, IX and X are synthesized in liver as inactive proteins.
- These factors are rich in glutamic acid residues and are carboxylated in liver where active form of vitamin K acts as a cofactor.
- Vitamin K is converted to inactive epoxide form by oxidation and is regenerated to its active form by epoxide reductase enzyme.
- Warfarin is a coumarin derivative and has a structure similar to that of vitamin K.
- Hence, warfarin competitively inhibits epoxide reductase enzyme, thus inhibiting the synthesis of vitamin K-dependent biologically active factors—II, VII, IX and X
- and produces anticoagulant effect.
- The onset and duration of anticoagulant effect of warfarin depends on the half-lives (in hours) of clotting factors,
- which are as follows: VII (6), IX (24), X (36) and II (50).
- There is always a delay in the onset of anticoagulant effect because the levels of clotting factors already present in plasma decline slowly over a period of 1–3 days.
Pharmacokinetics

- Warfarin is almost **completely absorbed after oral administration.**
- It can also be given **intravenously or rectally.**
- **Food interferes** with the absorption of warfarin.
- It is **highly bound to plasma proteins**, freely **crosses placental barrier**, is metabolized in **liver** and the inactive metabolites are **excreted in urine** and stool.
- It has a **long half-life of about 40 hours**, and the duration of action is **2–5 days**.

Adverse effects

1. **Bleeding**
   - Bleeding can be controlled by **oral or parenteral vitamin K1**
   - Oral anticoagulant therapy is monitored by measuring international normalized ratio (INR).

2. **Teratogenic effect:** Warfarin is **contraindicated during pregnancy** as it may cause **foetal CNS abnormalities, foetal haemorrhage, abortion or intrauterine death.**

3. **Skin necrosis**—The skin lesions are commonly seen on **breast, buttocks, abdomen and thighs.**
4. **Other rare side effects:** These include **diarrhoea, alopecia, urticaria, dermatitis, abdominal cramps** and anorexia.

Oral direct thrombin inhibitor

- Dabigatran etexilate is a prodrug, which is converted to dabigatran.
- **No laboratory monitoring is required during dabigatran therapy.**
## Difference between heparin and warfarin

<table>
<thead>
<tr>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Naturally occurring: animal source—ox lung, pig intestine</td>
<td>Synthetic</td>
</tr>
<tr>
<td>2. Active in vivo and in vitro</td>
<td>Active only in vivo</td>
</tr>
<tr>
<td>3. Administered parenterally (i.v., s.c.)</td>
<td>Administered orally</td>
</tr>
<tr>
<td>4. Acts by activating antithrombin III and inactivates Xa, Ila, IXa, Xla, XIIa and XIIIa</td>
<td>Acts by inhibiting synthesis and carboxylation of vitamin K-dependent clotting factors II, VII, IX and X</td>
</tr>
<tr>
<td>5. Has a rapid onset, but short duration of action (3–6 h)</td>
<td>Has a delayed onset, but long duration of action (3–6 days)</td>
</tr>
<tr>
<td>6. Heparin therapy is monitored by measuring aPTT</td>
<td>Therapy is monitored by measuring INR</td>
</tr>
<tr>
<td>7. Overdosage is treated with protamine sulphate (antagonist)</td>
<td>Overdosage is treated with fresh frozen plasma and vitamin K₃</td>
</tr>
<tr>
<td>8. Does not cross the placental barrier and is safe during pregnancy</td>
<td>Crosses the placental barrier and has teratogenic potential</td>
</tr>
<tr>
<td>9. Used mainly to initiate therapy</td>
<td>Used for maintenance therapy</td>
</tr>
<tr>
<td>10. Expensive</td>
<td>Not expensive</td>
</tr>
</tbody>
</table>
Therapeutic Uses of Anticoagulants

- The main aim of anticoagulant therapy is to prevent formation of intravascular thrombus or further extension of the already formed clot.
- They do not dissolve the clot or thrombus once it is formed.

- Treatment is initiated with an LMWH or UFH and continued for at least 4–5 days.
- An oral anticoagulant, warfarin, is usually started simultaneously as it has a delayed onset of action.

1. Deep vein thrombosis and pulmonary embolism:
   - Venous thrombi are mainly formed of fibrin.
   - Anticoagulants are used for the treatment and prevention of thromboembolism in high-risk cases, e.g. prolonged hospitalization, prolonged immobilization, major surgery, major trauma, etc.
   - Anticoagulants are used along with low-dose aspirin to prevent thromboembolism in patients undergoing haemodialysis and those with prosthetic heart valves.

2. Myocardial infarction:
   - Anticoagulants (heparin, LMWH or fondaparinux) are used in patients with a high risk of embolism
   - Anticoagulants help to prevent recurrent attacks of myocardial infarction and stroke, especially when given in combination with low dose of aspirin.
   - Heparin is used during coronary angioplasty.

3. Unstable angina

4. Atrial fibrillation

5. disseminated intravascular coagulation.
Fibrinolytics (Thrombolytics)

Fibrinolytics promote the conversion of plasminogen to plasmin.

- Plasmin degrades fibrin into fibrin degradation products and thus rapidly dissolves the blood clot.
- Streptokinase, urokinase, alteplase, reteplase and tenecteplase are plasminogen activators.
- Reteplase and tenecteplase are obtained from DNA recombinant technology. They have longer plasma half-lives than alteplase.

**Uses of fibrinolytics**

1. **Acute MI:**
   - The main aim of fibrinolytic therapy is to restore coronary artery patency.
   - Thrombolytic therapy is more effective if they are administered within 6–12 h of onset of symptoms.

2. **Deep vein thrombosis:** Thrombolytic therapy helps to prevent DVT.

3. **Pulmonary embolism:** Fibrinolytics are used to lyse the clot.

**Contraindications**

- Recent trauma, recent surgery, recent abortion, recent stroke, severe hypertension
- Severe diabetes, severe liver damage, peptic ulcer and bleeding disorders.
<table>
<thead>
<tr>
<th><strong>Streptokinase</strong></th>
<th><strong>Urokinase</strong></th>
<th><strong>Alteplase (t-PA)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. It is a protein derived from β-haemolytic streptococci</td>
<td>It is an enzyme isolated from human foetal kidney cell culture</td>
<td>It is derived from recombinant DNA technology</td>
</tr>
<tr>
<td>2. Streptokinase binds with circulating plasminogen to form a complex that activates plasminogen to plasmin</td>
<td>It directly activates plasminogen to plasmin</td>
<td>It selectively activates plasminogen that is bound to fibrin and avoids the activation of circulating plasminogen</td>
</tr>
<tr>
<td>3. Streptokinase is:</td>
<td>Urokinase is:</td>
<td>Alteplase is:</td>
</tr>
<tr>
<td>• Antigenic</td>
<td>• Nonantigenic</td>
<td>• Nonantigenic</td>
</tr>
<tr>
<td>• Pyrogenic</td>
<td>• Not destroyed by antibodies</td>
<td>• Nonpyrogenic</td>
</tr>
<tr>
<td>• Destroyed by circulating antistreptococcal antibodies</td>
<td></td>
<td>• Not destroyed by antibodies</td>
</tr>
<tr>
<td>4. Administered by i.v. infusion</td>
<td>Administered initially as i.v. bolus, followed by i.v. infusion</td>
<td>Administered initially as i.v. bolus, followed by i.v. infusion</td>
</tr>
<tr>
<td>5. Adverse effects: Bleeding, hypotension, allergic reactions like fever, chills, skin rashes and rarely anaphylactoid reaction</td>
<td>Bleeding can occur; but hypotension and allergic reactions are rare</td>
<td>Lower risk of bleeding and allergic reactions</td>
</tr>
</tbody>
</table>
Antifibrinolytics

Antifibrinolytics block the conversion of plasminogen to plasmin and thus inhibit fibrinolytic activity.

Epsilon amino-caproic acid (EACA)
- It is administered orally or intravenously.
- It is used mainly to control bleeding due to overdose of fibrinolytics after tooth extraction and surgery in haemophiliacs.
- It can also be used in haematuria and bleeding following obstetric complications.
- It rarely causes myopathy and muscle necrosis.

Tranexamic acid
- It is available for oral, i.v. and topical administration.
- It is more potent than EACA.
- It is used to control bleeding due to excessive fibrinolytic activity and following tooth extraction, tonsillectomy, prostatectomy, etc.
- In dentistry, tranexamic acid soaked gauze or mouthwash can be used to reduce bleeding postoperatively in haemophiliacs and in patients on anticoagulant therapy.
- Its main side effects are nausea, vomiting, diarrhoea, headache, etc.
ANTIPLATELET DRUGS

Drugs that inhibit platelet aggregation are called antiplatelet drugs

**Classification**

1. **Thromboxane (TXA2) synthesis inhibitor** Low-dose aspirin.
2. **Phosphodiesterase inhibitor** Dipyridamole.
3. **Thienopyridine derivatives** Ticlopidine and clopidogrel.
4. **Glycoprotein (GP)-IIb/IIIa-receptor antagonists**: Abciximab, eptifibatide and tirofiban.
Aspirin (TXA2 synthesis inhibitor)
- Low-dose aspirin (50–325 mg) irreversibly acetylates platelet COX-I and reduces the production of TXA2;
- thus the antiplatelet effect lasts for the life-time of the platelets, i.e. 7–10 days.
- In higher doses, aspirin inhibits both TXA2 and PGI2; hence efficacy is reduced.
- Common adverse effects are gastric irritation and bleeding.

Dipyridamole (phosphodiesterase inhibitor)
- It is a vasodilator.
- It inhibits phosphodiesterase and increases the concentration of cyclic adenosine monophosphate (cAMP) levels, which inhibits platelet aggregation.
- It is occasionally used in combination with warfarin during postoperative period in patients with prosthetic heart valves.

Ticlopidine and clopidogrel (thienopyridine derivatives)
- They are prodrugs and structurally related.
- They inhibit adenosine diphosphate (ADP)-mediated platelet aggregation.
- Ticlopidine is well absorbed after oral administration and is converted to an active metabolite in liver.
- It has a long duration of antiplatelet effect.

- Side effects are nausea, vomiting, diarrhoea, leucopaenia, agranulocytosis, thrombocytopaenia and GI bleeding.

Clopidogrel
- It is a congener of ticlopidine.
- It is also given orally.
- They produce synergistic effect when combined with aspirin or GP-IIb/IIIa antagonists.
- Clopidogrel produces fewer side effects than ticlopidine; and it rarely produces neutropaenia and thrombocytopaenia.
Abciximab, eptifibatide and tirofiban (GP IIb/IIIa receptor antagonists)

- They block GP IIb/IIIa receptors for fibrinogen and von Willebrand’s factor on platelet surface,
- Thus inhibiting the final step in the process of platelet aggregation.
- These drugs are administered parenterally.
- Abciximab is a monoclonal antibody
- Eptifibatide is a synthetic drug.

The main side effect of these drugs is bleeding.

Uses

- Acute MI: Low-dose aspirin is most commonly used in high-risk individuals to reduce the incidence of MI and in post-MI patients to prevent recurrent attacks.
- unstable angina,
- Transient ischaemic attacks,
- in patients with prosthetic heart valves
- Peripheral artery Disease.
HAEMATINICS

Causes of anaemia
1. **Decreased formation of RBCs:** Deficiency of essential nutrients—iron, vitamin B12, folic acid, etc.
2. **Increased destruction of RBCs:** Haemolytic anaemias, sickle-cell anaemia.
3. **Depression of bone marrow:** Cytotoxic drugs, radiation, toxins.
4. **Excessive blood loss:** Due to hookworm infestation, bleeding from gastrointestinal tract (GIT) and other sites.

Iron

Iron is an essential element of the body.

➢ The important sources of iron are liver, fish, dry fruits, jaggery, spinach, banana, meat, etc.
Factors affecting iron absorption
- Iron absorption is facilitated by **acidic pH of the stomach, ascorbic acid, cysteine, etc.**, which reduces the ferric iron to ferrous form.
- Iron-deficiency states also increase the absorption of iron.
- Iron absorption is inhibited by **excess of phosphates, oxalates, phytates, etc.**
- Milk, antacids and tetracyclines reduce iron absorption by forming insoluble complexes.

Preparations of iron

**Oral preparations:**
1. Ferrous sulphate contains 20% (hydrated salt) and 32% (dried salt) elemental iron.
   - It is the oldest and cheapest iron preparation.
2. Ferrous gluconate contains 12% elemental iron.
3. Ferrous fumarate contains 33% elemental iron.
4. Colloidal ferric hydroxide – 50%
5. Carbonyl iron – Purified metallic iron

Other are ferrous succinate, iron choline citrate, ferric ammonium citrate, etc.

**Adverse effects of oral iron are** - nausea, vomiting, epigastric discomfort, dyspepsia, metallic taste, constipation or diarrhoea, and staining of teeth (mainly with liquid preparation).

**Parenteral preparations**
1. Iron sorbitol citric acid complex (Jectofer): It is given intramuscularly, but never intravenously.
2. Iron dextran complex (Imferon): It can be administered intravenously or intramuscularly.
   - To prevent staining of the skin, intramuscular injection of iron preparations into the buttock is made using Z-track technique.
3. Ferric carboxymaltose and ferrous sucrose are administered intravenously. The risk of hypersensitivity reaction is much less with these preparations.
**Indications for parenteral iron therapy**
1. Intolerance to oral iron.
2. Severe malabsorption.
3. Non-compliance to oral iron.
4. Severe anaemia in the late stages of pregnancy.
5. Along with erythropoietin in patients with renal disease.

The total dose of parenteral iron is calculated by using the formula

$$\text{Iron requirement (mg)} = 4.4 \times \text{body weight (kg)} \times \text{Hb deficit (g/dL)}$$

(Normal Hb in men = 14–16 g%; women = 12–14 g%)

**Adverse effects**
- The injections are painful,
- May cause abscess and discolouration of the skin at the site of injection.
- The systemic side effects are **headache, pyrexia, nausea, vomiting, arthralgia, lymphadenopathy, urticaria**
- An anaphylactic reaction (Test dose of iron preparation should be administered before giving full dose of parenteral iron).

**Therapeutic uses of iron**
1. To treat iron-deficiency anaemia (microcytic hypochromic anaemia)
   a. During pregnancy.
   b. Due to blood loss.
   c. Due to nutritional iron deficiency.
   d. Due to poor absorption of iron from the gut.

- Most of the patients can be treated with oral iron.
- For treatment of iron-deficiency anaemia, 200 mg of elemental iron is required per day.
- Ferrous sulphate is the most commonly used preparation—200 mg of ferrous sulphate (60 mg elemental iron) is given thrice daily after food.
- **Therapy should be continued till the Hb level returns to normal (4–8 weeks);**
- and later, iron should be continued for at least 3–6 months to replenish iron stores.
- The expected rise in Hb concentration after iron therapy is 0.7–1 g/100 mL/week.
2. Prophylaxis
- Prophylactic iron therapy is usually indicated during pregnancy and infancy.
- For prophylaxis, **100 mg of elemental iron is administered daily**
- Starting from the second trimester.
- Folic acid 0.5 mg/day is given from the first trimester to prevent neural tube defects.

Acute Iron Poisoning
- It is seen frequently in young children.
- The manifestations are nausea, vomiting, epigastric pain, **bloody diarrhoea**, dehydration, cyanosis, drowsiness, hyperventilation, **metabolic acidosis**, convulsions, coma and death.

Treatment
General measures
Supportive measures
Airway, Breathing, Circulation, Fluid and Electrolyte and acid–base balance should be maintained.
- Whole bowel irrigation to remove unabsorbed iron pills from the GIT.
- Intravenous Diazepam to control convulsions.

Specific therapy
- Desferrioxamine, a potent iron chelating agent
- It is administered **by i.v. infusion or intramuscularly** depending on the severity of poisoning.
- It binds with **iron in the blood and facilitates its excretion**.