Pharmacology of Hematopoietic & Lymphatic System

by

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HEMATOPOIETIC & LYMPHATIC SYSTEM PHARMACOLOGY

DRUG THERAPY OF ANEMIAS

- Anemia is defined as a low hemoglobin (Hb) concentration due to reduced production or increased loss of RBC. The WHO defines anemia as Hb <13 g/dL in men or <12 g/dL in women.

Types of anemia:

1. **Deficiency Anemia:**
   - Normal erythropoiesis requires certain exogenous substances (iron, folic acid & vitamin B_{12}) & some endogenous factors (intrinsic factor, erythropoietin & colony stimulating factors).
   - Iron deficiency anemia: due to iron deficiency
   - Megaloblastic anemia: due to vitamin B_{12}, intrinsic factor, or folic acid deficiency.
2. **Aplastic anemia:** due to damage of bone marrow
3. **Hemolytic anemia**: due to destruction of red cells

DRUG THERAPY OF IRON-DEFICIENCY ANEMIA

(Microcytic Hypochromic Anemia)

IRON

Iron Absorption

- Iron intake occurs from plant-derived foods, in the form of non-heme iron (Fe^{3+}, ferric), and from animal-derived foods, in the form of heme iron (Fe^{2+}, ferrous)
- Absorption occurs in the duodenum and in the first portion of the jejunum (acid medium ↑ solubility).
- **Fe^{2+}** is directly taken up into the enterocyte (by the heme transporter)

- **Fe^{3+}** $\xrightarrow{\text{duodenal cytochrome-B (Dcytb)/cytochrome-b reductase-1}}$ Fe^{2+} which is taken up into the enterocyte (via divalent iron metal transporter-1; DMT1)
- Fe^{2+} + apoferritin → ferritin (the cellular store of iron), so saturation of apoferritin will limit further absorption (mucosal block)

Factors Enhancing Iron Absorption

1. Infancy, adolescence and in iron-deficiency anemia (↑ demand)
2. Ascrobic acid, HCl & succinic acid → ↑ absorption (ferric → ferrous).

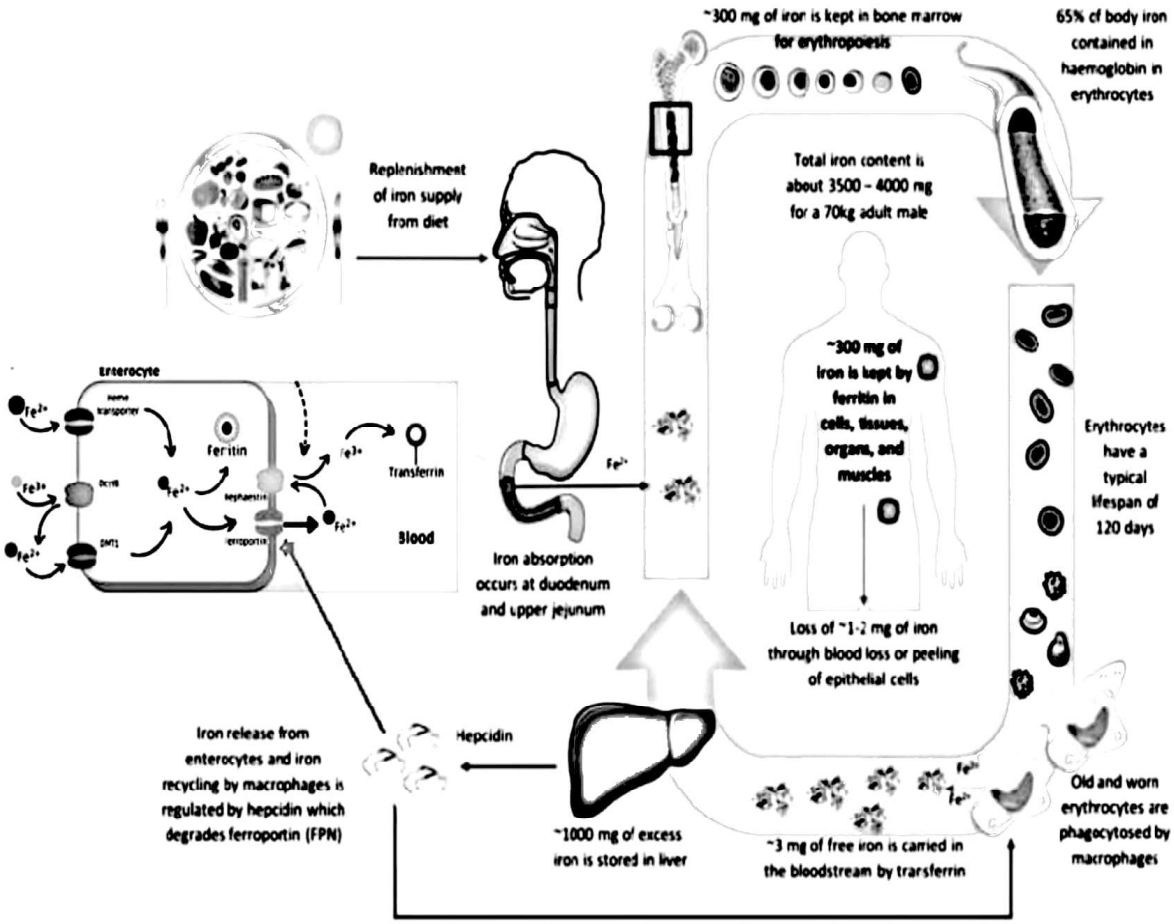
Factors Reducing Iron Absorption

1. Gastric resection and malabsorption syndrome.
2. Desferrioxamine (chelates iron).
3. Antacids.
4. Tannic acid (precipitates iron).
5. Ca in dairy food→ ↓ iron absorption
5. Tetracyclines & iron bind together → ↓ absorption of both.
6. Phosphates & oxalates (form insoluble iron complexes).

[N.B. Foods that decrease non-heme iron absorption have little effect on absorption of heme iron.]

Iron Transport:

- By the ferroportin transporter, Fe^{2+} is carried from the enterocyte into the blood stream
- Fe^{2+} is re-oxidized by the enzyme hephaestin in mucosal cells → Fe^{3+}
- Fe^{3+} is transported in blood as transferrin to all other tissues in the body and stored in the liver, reticuloendothelial system and bone marrow as ferritin.
- Hepcidin (a protein synthesized by the liver) regulates iron release from enterocytes and iron recycling by macrophages, and it may contribute to the anemia of chronic diseases.



Indications of Iron Therapy

1- Prophylactic of the occurrence of iron-deficiency anemia (IDA):

30-60 mg/day elemental iron

2- Treatment of IDA: **200-400 mg/d elemental iron** in 2-3 divided doses/d

(Elemental iron is the total amount of iron in the supplement available for absorption. In Fe deficient individuals, about 50-100 mg of Fe can be incorporated into hemoglobin daily, and about 25% of oral Fe given can be absorbed).

Iron-Deficiency Anemia due to: (Treatment of the cause is essential).

1. ↑ **Demand**: premature infants, children, pregnant and lactating women.
2. ↓ **Absorption**: after gastrectomy & in malabsorption syndrome.
3. **Chronic blood loss**: e.g., occult GIT bleeding, heavy menstrual bleeding, during hemodialysis, ancylostomiasis.
4. ↑ **in blood formation**: during treatment of severe pernicious anemia with vitamin B_{12} (depletion of iron stores), during treatment with erythropoietin (formation of RBCs at a high rate).

Iron Therapy (Oral – Parenteral (IV, IM)

I. Oral Iron Therapy

- Effective & cheap (treatment of choice).
- Oral preparations include **ferrous sulfate, gluconate** and **fumarate**.
- Given after meals to decrease GIT disturbances.
- **New agents**: **polysaccharide-iron complex**, **carbonyl iron**. **Heme iron polypeptide**: More expensive.
- Different Fe salts provide different amounts of elemental Fe:

Iron formulation	**ferrous gluconate**	**ferrous sulfate**	**ferrous fumarate**	**polysaccharide-iron complex**	**Carbonyl iron**
Elemental iron	**12%**	**20%**	**33%**	**100%**	**100%**

- Continue iron till Hb is normal (1-2 months) & for an extra 2-4 months to replenish stores.

Iron salts are usually used as ferrous iron is efficiently absorbed.

Adverse Effects of Oral Iron Therapy

1. GIT disturbances: nausea, epigastric pain, constipation (given after meals - start with small dose then gradually increase).
2. Black stools (mask diagnosis of GI bleeding).
3. Black staining of teeth (iron sulfide in mouth).

II. Parenteral Iron Therapy

Indications (= Causes of failure of oral iron therapy)

1. Noncompliance to oral therapy (severe GIT disturbance or ulceration).
2. Malabsorption syndrome causes failure of iron absorption.
3. Severe anemia, e.g. in malignancy.

Calculation of Parentral Iron
(to correct anemia & replenish stores)

Total iron deficit (mg) =
Body weight (kg) x [Target Hb - Actual Hb] (g/l) x 2.4 + 500 (mg)

Parenteral Iron Preparations

A) Iron dextran

B) Iron sucrose complex & Iron sodium gluconate complex.

C) Newer preparations: Ferric carboxymaltose & Ferumoxytol

- Given by **deep IMI** or by **IV infusion** (as a total dose infusion, **TDI**).

Advantages of TDI

1) Avoids non-compliance of the patient.
2) Avoids unpleasant effects of IMI.
3) Allows delivery of the entire dose of iron necessary to correct iron deficiency at one time.
    - ❖ The initial 25 ml should be infused slowly (as a test dose) and the patient should be observed for allergic reaction.

Adverse Reactions of parenteral iron therapy

- **IM:** local pain - tissue staining.
- **IV:** headache, fever, urticaria, lymphadenopathy & anaphylactic shock.

Monitoring iron therapy:

A. Clinically: improve the patient's symptoms and signs.
B. Lab. Investigations:
    1. Reticulocyte counts: ↑ (1 week)
    2. Hb: ↑ (1 gm/10-15 days)
    3. Serum ferritin: > 50 ug/dl (stores) (after 4-6 months)

Iron Toxicity

Acute Iron Toxicity (more in children)

A. GIT (up to **1h**): Abdominal pain- nausea- vomiting- bloody diarrhea.
B. Shock & lethargy (up to **6h**): dyspnea- cardiovascular collapse
C. Improvement (up to **6-12h**): as iron is absorbed into blood.
D. Systemic (up to **12-60h**): metabolic acidosis- convulsions- coma & death.

Treatment (urgent and immediate)

1. Raw egg or milk ➔ bind & precipitate iron as albuminate or caseinate until a chelating agent is available.
2. **Deferoxamine** (1-2 g IM or IV) ➔ chelates iron promoting its excretion in urine.
3. Gastric lavage with bicarbonate solution ➔ form insoluble iron salts.
   Then, **deferoxamine** (5 g in 100 ml water) swallowed or through stomach tube.
4. IV infusion of saline, dextrose or bicarbonate ➔ correct water & electrolyte disturbance.

Chronic Iron Toxicity

It occurs in:

1. Patients receiving many red cell transfusions.
2. Patients with hemochromatosis; an inherited disorder characterized by ↑ Fe absorption ➔ hemosiderosis (Fe^{3+} precipitation in vital organs).

Management

1. Venesection (if no anemia) ➔ repeated weekly (a single venesection of 500 ml blood removes 200 mg iron)
2. **Deferoxamine** IM or SC.
3. Large intake of tea ➔ tannins bind iron.

DRUG THERAPY OF MEGALOBLASTIC ANEMIA

(Vitamin B_{12} and Folic Acid Deficiency)

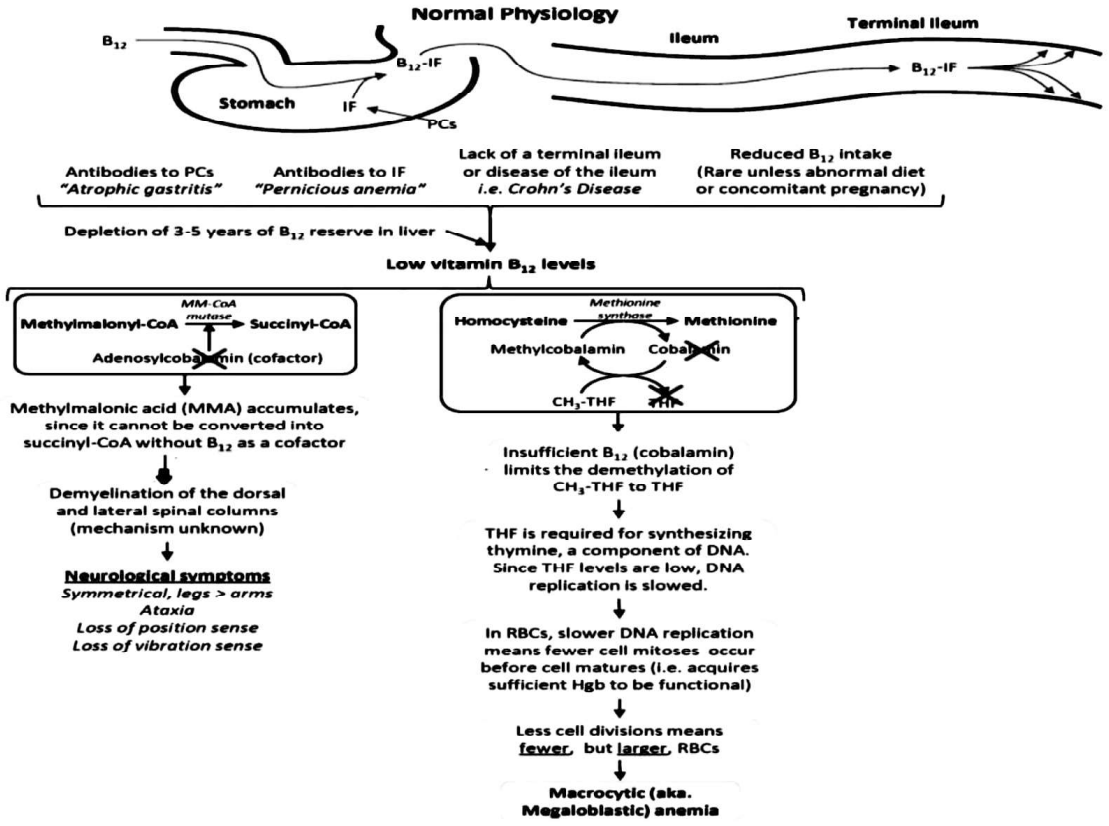
I. Vitamin B_{12}

- Cobalt-containing compound synthesized by bacterial flora in colon.
- Called extrinsic factor to differentiate it from an intrinsic factor (a glycoprotein formed by parietal cells, necessary for vitamin B_{12} absorption).

Functions of Vitamin B_{12}: It is essential for:

1. Cell growth and replication (DNA synthesis).
2. Maintenance of normal myelin sheath, erythropoiesis and cell maturation.
3. Normal metabolic functions of folate.

If vitamin B_{12} absorption is stopped, it takes 5 years for megaloblastic anemia to develop since its daily requirement is 2 μg & body store is relatively high.



Causes of Vitamin B_{12} deficiency:

1. Decreased intake (rare)
2. Decreased absorption:
   a. Decreased intrinsic factor (pernicious anemia)
   b. Terminal ileum disease e.g. Crohn's disease.
   c. **Drugs:** Neomycin, colchicine and antiepileptics
3. Increased demands: pregnancy, chronic hemolysis
4. Increased consumption: Diphyllobothrium latum

Pernicious Anemia

- It is a severe form of megaloblastic anemia due to deficiency of intrinsic factor (congenital, autoimmune, after gastrectomy). The disease is characterized by:
  1. Megaloblastic anemia (large red cells highly susceptible to destruction).
  2. Subacute combined degeneration of brain, spinal cord & peripheral nerves.
  3. Atrophic gastritis.

Preparations of Vitamin B_{12}

A. Cyanocobalamin

B. Hydroxocobalamin (preparation of choice):

1. More slowly absorbed.
2. More bound to plasma proteins.
3. Slowly excreted.
4. More sustained rise in serum cobalamin.

Therapeutic uses of Vitamin B_{12}

A. Megaloblatic Anemia (plus Folic acid 5 mg/d) [**treatment of the cause**]

1. Pernicious anemia: vitamin B_{12} is given for life by IMI.

- Initial therapy: 1000 μg/day for 1-2 week to replenish stores.
- Then 1000 μg/week till normal blood count.
- Then Maintenance therapy: 1000 μg/month for life.

2. Megaloblastic anemia due to diphylobothriasis (vitamin B_{12} + praziquantel).

3. Drug-induced megaloblastic anemia

NEVER give folic acid alone in B_{12} deficiency as it ↑↑↑↑ the neurological complications

B. Neurological Conditions

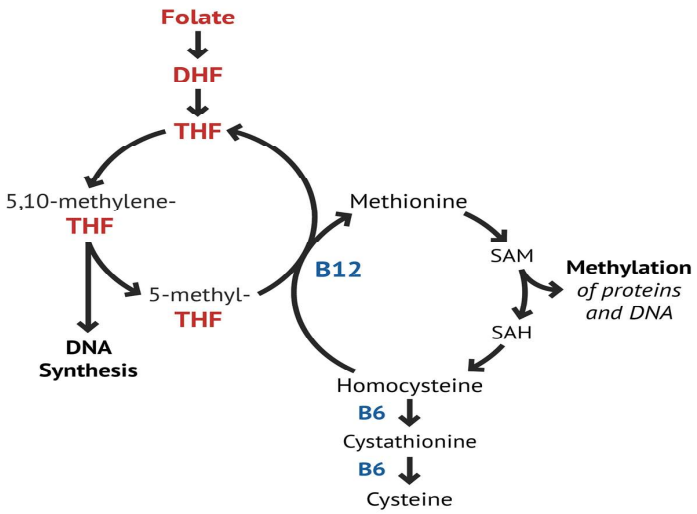
- Peripheral neuritis in diabetes & retrobulbar neuritis in heavy smokers.

II. Folic Acid

(Pteroylglutamic Acid)

- **Source:** liver, yeast and green vegetables.
- Essential for DNA synthesis.
- Vitamin B_{12} is essential for activation of folic acid. So vitamin B_{12} deficiency is often associated with folic-acid-deficiency anemia.
- No neurological abnormalities are associated with folate deficiency.

Folate deficiency develops more rapidly than vitamin B_{12} deficiency since daily requirement is high and body store of folate is low.



Causes of Folic Acid Deficiency

1. Inadequate dietary supply (common)
2. Increased demand: e.g. pregnancy, lactation.
3. Decreased absorption: malabsorption syndrome.
4. **Drug-induced folic acid deficiency:**
   a. Antiepileptics & oral contraceptives (interfere with folate absorption).
   b. Methotrexate, sulphonamides (inhibit dihydrofolate reductase enzyme) **[Treated by folinic acid].**

Therapeutic uses of folic Acid

1. Nutritional megaloblastic anemia.
2. Malabsorption syndrome.
3. In alcoholics and pregnant women.
4. Patients with liver disease & with hemolytic anemia.
5. With anticonvulsant drugs.
6. Patients on dialysis (as folic acid is removed each time).

Anemia of chronic disease

- It is a functional iron deficiency anemia.
- Chronic infection and inflammation with → ↑ release of cytokines → stimulate the release of hepcidin from the liver → prevent absorption & release of iron from its storage sites (sequestrated anemia).
- Differs from iron deficiency anemia → there is **normal or high serum ferritin.**
- Not treated with iron but its treatment is to treat infection & inflammation.

Treatment of Aplastic anemia

1. **Blood transfusion** to replace lacking components.
2. Treatment according to **cause** (if known).
3. **Corticosteroids**: reduce bleeding caused by thrombocytopenia.
4. **Broad-spectrum antibiotics**, e.g. penicillins to treat infections.
5. **Bone marrow transplantation** (treatment of choice) followed by **immunosuppression** to prevent graft rejection.
6. **Erythropoietin**. (IV or SC)
   - Regulator of erythropoiesis (acts on stem cells).
   - Used in anemia of chronic renal failure & severe anemia of cancer & AIDS.
   - It decreases the need for transfusion as it elevates red blood cell level.

DRUG THERAPY OF THROMBOSIS

Thrombosis:

- Thrombosis is a pathological condition resulting from inappropriate activation of the hemostatic mechanisms i.e. platelet aggregation & coagulation (fibrin formation).

MECHANISMS OF BLOOD COAGULATION:

A. In the absence of injury of vesseles:

- Resting platelets circulate freely and platelet activation and aggregation are not initiated due to:

1. Chemical mediators (synthesized by endothelial cells):

- Prostacyclin (PGI_2): binds to its platelet membrane receptors →↑ intracellular cAMP →↓ free intracellular Ca^{++}
- Nitric oxide (NO): binds to its platelet membrane receptors → ↑ intracellular cGMP →↓ free intracellular Ca++
  - ↓ free intracellular Ca^{++} →
    - Inhibits release of platelet aggregation agents from granules
    - Stabilizes inactive GPIIb/IIIa receptors.
    - ↓ synthesis of TXA_2

2. **The intact endothelium** covers subendothelial collagen and circulating **levels of thrombin and TXA_2** are low.

B. In response to vascular injury:

1. Vasospasm of injured blood vessel.

2. Platelets functions:

- **Platelets adhesion:** platelets stick to collagen and von Willebrand factor (vWf) released at area of injury → a complex series of chemical reactions → platelet activation.

- **Platelets activation:** - Activated platelets release chemicals such as:
  - ADP →↓ intracellular cAMP → ↑ free intracellular Ca^{++} → platlets activation and aggregation
  - $Thromboxane_{A2}$ (synthesized by COX-I enzyme) → platlets aggregation.
  - Serotonin → further potentiates vasoconstriction
  - PAF

  - Activated platelets also express on their surface:
    - Certain proteins (receptors) that attach to:
      - vWf (synthesized by the endothelium of blood vessels)
      - fibrinogen (glycoprotein IIb/IIIa)
      - collagen (glycoprotein Ia)
    - A crucial clotting protein called thrombin.
- **Platelets aggregation:**

  - The activation of platelets → release of sequestered Ca^{++} stores → ↑ free intracellular Ca^{++} →
    - Release of platelet aggregation agents from granules
    - Active of GPIIb/IIIa receptors that bind fibrinogen
    - Activation of TXA2
  - Fibrinogen (a soluble plasma GP) → binds to GPIIb/IIIa receptors on two separate platelets → platelet cross-linking and platelet aggregation → each activated platelet can recruit other platelets
- **Platelets plug**: platelets loss their individual membrane forming gelatinous mass → arrest bleeding.

3. Fibrin clott:.

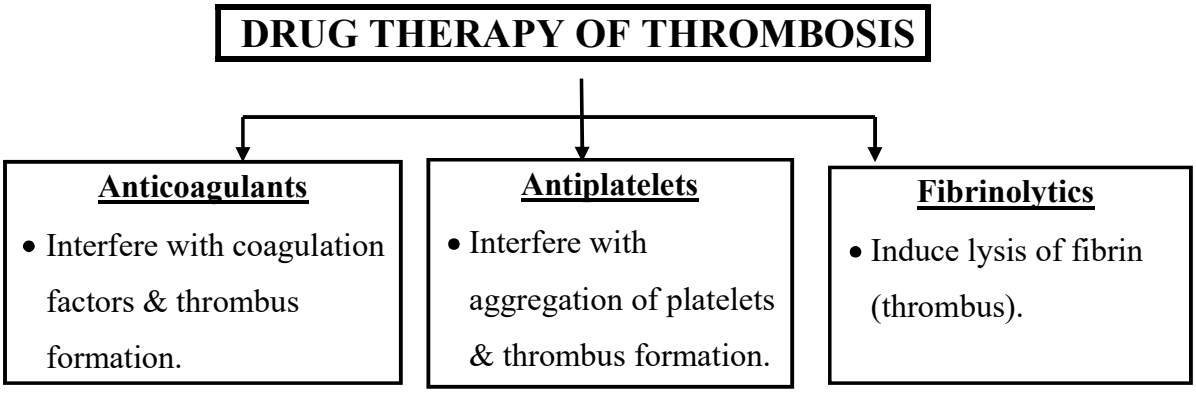
- Tissue factors (from the injured tissue) + mediators (on the surface of platelets) → local stimulation of the clotting cascade → formation of thrombin (factor lla) → hydrolysis of fibrinogen to fibrin → the platelet plug is reinforced by fibrin.

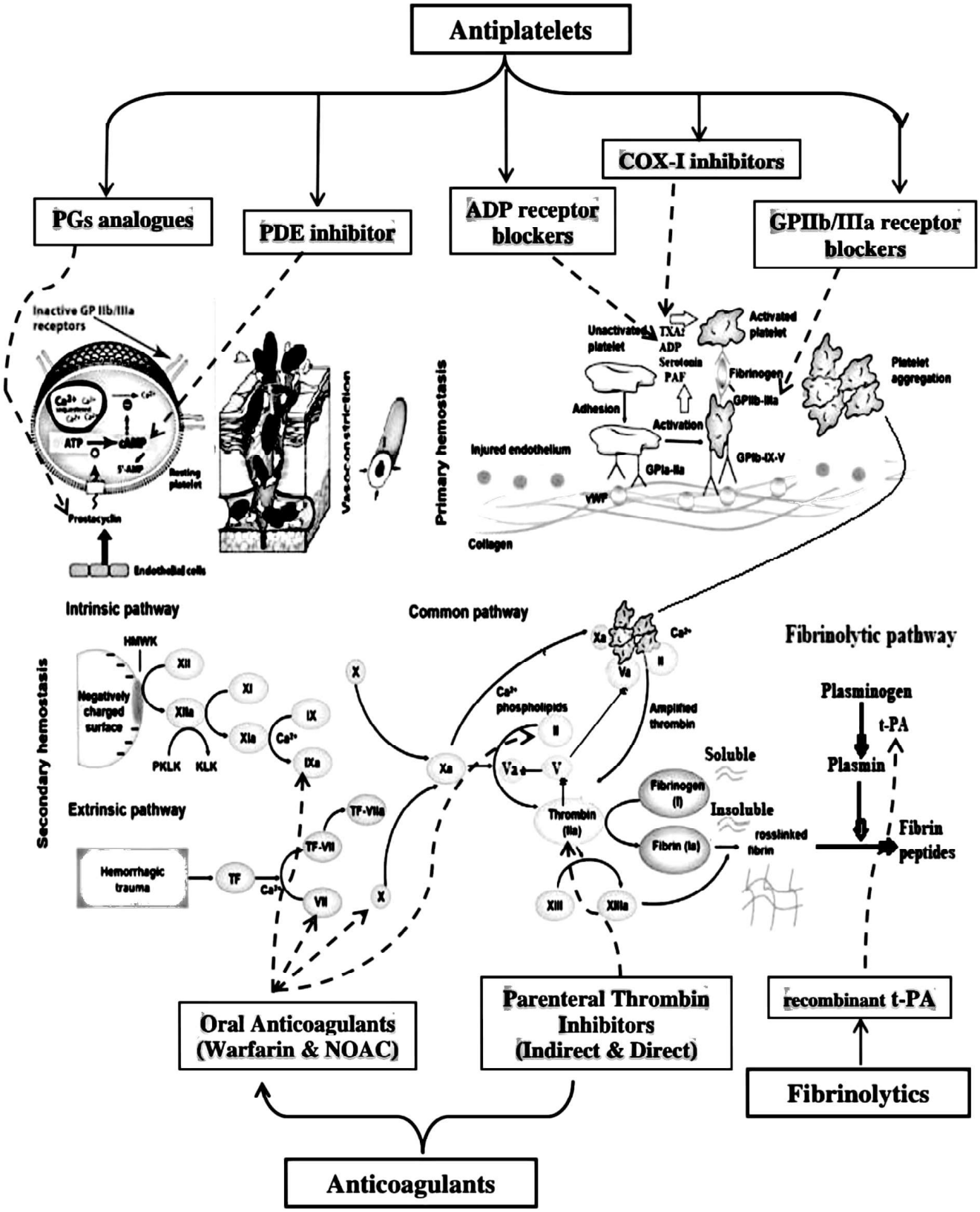
- Subsequent cross-linking of the fibrin strands stabilizes the clot.

4. Fibrinolysis: Tissue plasminogen activator (t-PA) → activation of plasminogen to plasmin → splits fibrin and fibrinogen into fragments → clot dissolution.

There are 2 types of thrombus:

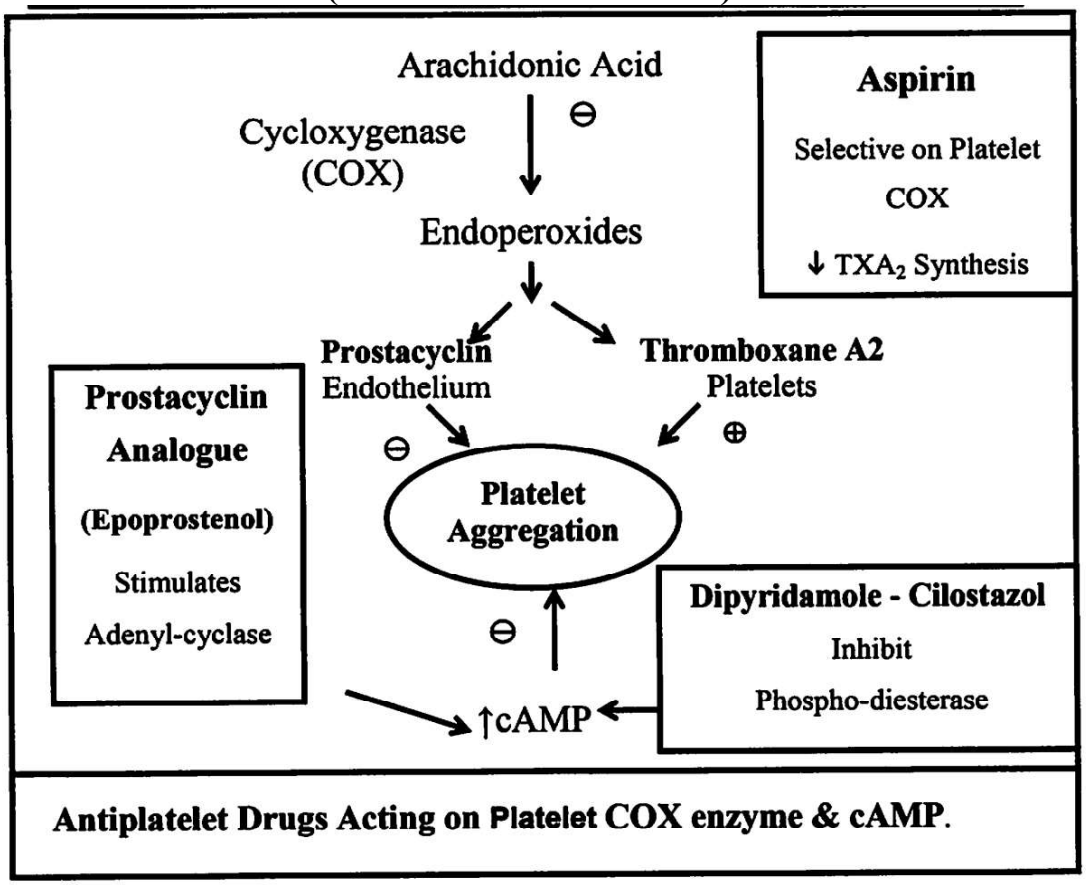
1. **White thrombus**: formed in arteries due to platelets adhesion. High pressure circulation leads to vessels injury.
   - Risk factors: smoking, hypertension, hyperlipidemia, diabetes mellitus, cholesterol emboli
   - e.g. coronary thrombosis, cerebral thrombosis, peripheral artery thrombosis/ embolism.
   - Treated mainly by antiplatelet drugs & fibrinolytics.
2. **Red thrombus:** formed in veins due to venous stasis which triggers fibrin network formation through which red cells are enmeshed forming the red thrombus.
   - Risk factors: pregnancy, immediate post-childbirth period, use of oral contraceptives or estrogen replacement therapy, high dose corticosteroid therapy, immobilization (bone fracture, knee, hip, abdominal surgery, and catheters).
   - It increases in size with time forming long tail. This tail can be detached easily forming emboli e.g. pulmonary embolism.
   - Treated mainly by anticoagulants.(fibrinolytics may be used)



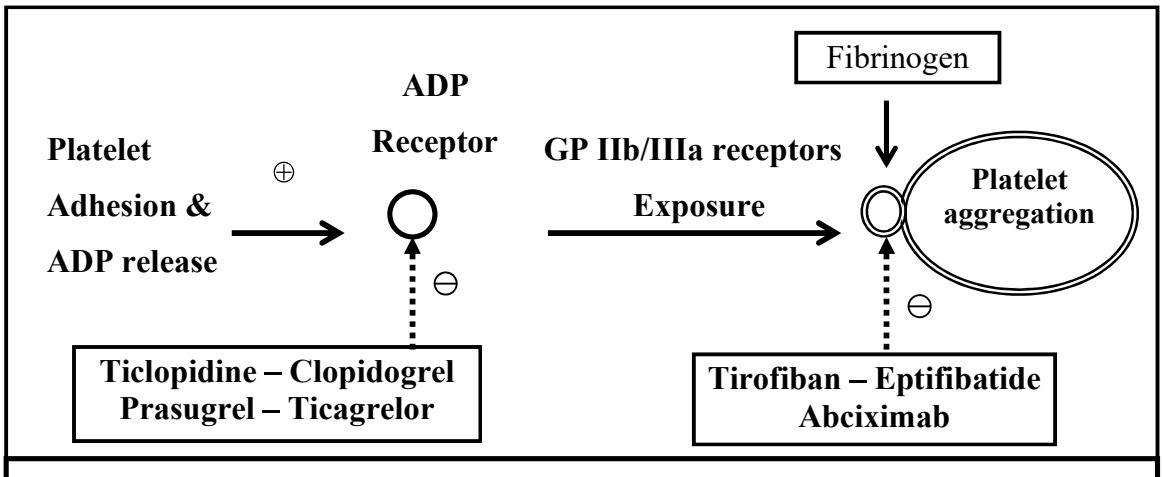

Antiplatelets
PGs analogues
PDE inhibitor
ADP receptor blockers
COX-I inhibitors
GPIIb/IIIa receptor blockers
Inactive GP IIb/IIIa receptors
ATP
cAMP
5'-AMP
Resting platelet
Prostacyclin
Endothelial cells
Vasoconstriction
Primary hemostasis
Unactivated platelet
TXA2
ADP
Serotonin
PAF
Activated platelet
Fibrinogen
GPIIb-IIIa
Platelet aggregation
Adhesion
Activation
Injured endothelium
GPIa-IIa
GPIb-IX-V
VWF
Collagen
Intrinsic pathway
Common pathway
Fibrinolytic pathway
Secondary hemostasis
HMWK
XII
XI
XIIa
XIa
IX
IXa
PKLK
KLK
Negatively charged surface
Extrinsic pathway
Hemorrhagic trauma
TF
TF-VII
TF-VIIa
VII
X
Xa
Va
Ca2+
Ca2+ phospholipids
Amplified thrombin
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
Soluble
Insoluble
rosslinked fibrin
Fibrin peptides
XIII
XIIIa
Plasminogen
t-PA
Plasmin
Oral Anticoagulants (Warfarin & NOAC)
Parenteral Thrombin Inhibitors (Indirect & Direct)
recombinant t-PA
Fibrinolytics
Anticoagulants

ANTIPLATELET DRUGS

(ANTITHROMBOTICS)



Antiplatelet Drugs Acting on Platelet COX enzyme & cAMP.



Platelet Aggregation & Site of action of AntiplateleDrugs Acting on platelet Receptors

Classification of antiplatelets according to mechanism of Action

I. Drugs Acting on Platelet COX Enzyme

Acetylsalicylic acid (Aspirin)

- Prototype antithrombotic
- Low (infantile)-dose aspirin **(75 - 325 mg/day oral):** inhibits platelet thromboxane A2 synthesis by inhibiting (**irreversible** acetylation) of COX-I enzyme.
- Aspirin is the main antiplatelet drug used. (Clopidogrel or dipyridamole may be combined to it or given to the patients intolerant to it).
- Low dos aspirin is selective on platelets (why??)

II. Drugs Increasing cAMP

1. PGI_2 analogue (epoprostenol)

- Stimulates adenyl cyclase → ↑cAMP.
- Potent antiplatelet & vasodilator.
- Very short duration (minutes)→ given by IVI.
- **Uses**: **hemodialysis-cardiopulmonary bypass- pulmonary hypertension**

2. Dipyridamole & Cilostazol (oral)

- Inhibit phosphodiesterase →↓ cAMP breakdown → ↑cAMP.
- Vasodilator & antiplatelet.
- Dipyridamole is a weak antiplatelet →combined with warfarin or aspirin. (prefered to aspirin for combination with warfarin due to less bleeding).
- **Cilostazol is used** in **intermittent claudication**

III. Drugs acting on platelet Receptors

1. Drugs inhibiting ADP receptors

- They inhibit **(irreversibly)** the binding of ADP to its receptors →inhibit expression of fibrinogen receptors
- **Ticlopidine- clopidogrel - prasugrel – ticagrelor**
- Are given orally, maximum effect is achieved after 3-5 days (loading dose is required to achieve rapid maximal effect)

2. Drugs blocking GP IIb/IIIa (Fibrinogen) Receptor

- **Tirofiban, eptifibatide, abciximab** (mono-clonal antibody)
- All are given IVI; short term therapy.
- They block platelet GP IIb/IIIa receptors (activation of this receptor complex is the "final common pathway" for platelet aggregation)
- **Abciximab** consists of monoclonal antibodies which bind to receptors.
- **Eptifibatide,** and **tirofiban** are analogues to delta chain of fibrinogen which mediates binding of fibrinogen to GP IIb/IIIa receptors on platelets.

Therapeutic uses of antiplatelet drugs (mainly in arterial thrombosis)

1. High risk of myocardial infarction (AMI): e.g., previous attack or angina.
2. Acute coronary syndrome.
3. Coronary bypasses grafting, angioplasty & stent insertion (clopidogrel is routinely used).
4. Prosthetic heart valves: thrombo-embolism.
5. Transient ischemic attacks (TIAs)- thrombotic stroke.

Adverse effects of antiplatelet drugs:

A. Common: increased risk of bleeding

B. Individual:

1. **Aspirin (oral once /day)**:
   - GIT: gastric irritation, bleeding ulcers.
   - Precipitating attack of bronchial asthma.
2. **Epoprostenol (IVI)**: Flushing, headache, hypotension.
3. **Dipyridamole (oral): Steal phenomena** (↑cAMP → VD → shift blood from atherosclerotic vessels to healthy vessels) **-**dizziness- headache- GIT disturbance.
4. **Cilostazol (oral):**
   - Headache, dizziness - GIT upset: dyspepsia, diarrhea
   - VD → Tachycardia, palpitations, peripheral edema.
5. **Ticlopidine (oral):** bone marrow depression → **neutropenia**

6. **Prasugrel: (oral)**
    - Increased risk of bleeding (CI: in patients with history of TIA or stroke)
7. **Clopidogrel (oral once /day)** (preferred to ticlopidine; less risk of neutropenia)
    - Rash - Gastric irritation- diarrhea.
    - Clopidogrel is a prodrug → avoid with PPIs e.g. omeprazole as it inhibits its activation in liver by CYP450
8. **Ticagrelor:** shortness of breath
9. **Abciximab (IVI)**: thrombocytopenia, arrhythmia.

ANTICOAGULANTS

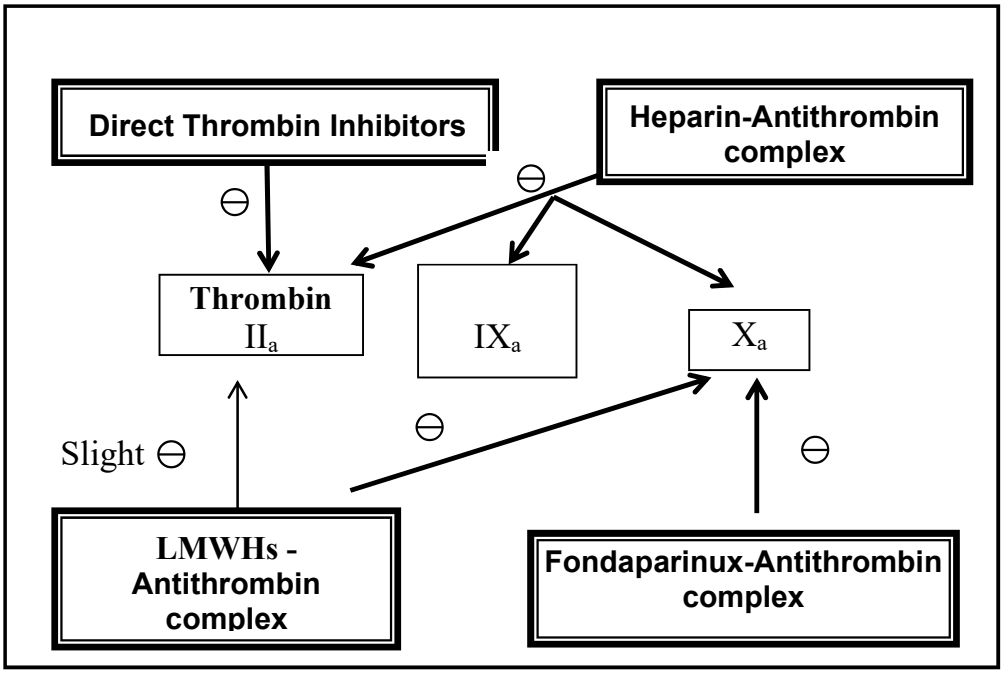
A. <u>Parenteral Anticoagulants:</u>

I. Indirect thrombin inhibitors: Heparin - low molecular weight heparins (LMWHs) - fondaparinux.

II. Direct thrombin inhibitors: Bivalirudin - Argatroban.

B. <u>Oral anticoagulants:</u> Warfarin – New oral anticoagulants (NOAC).

A.PARENTERAL ANTICOAGULANTS



Site of action of Indirect & Direct Thrombin Inhibitors

I. Indirect thrombin inhibitors:

1. Heparin (unfractionated heparin; UFH)

Chemistry

- Sulfated mucopolysaccharide with high MW **(HMWH)**
- Highly acidic with electronegative charge.
- Source: porcine intestinal mucosa and bovine lung

Pharmacological Actions

1. Anticoagulant action: (effective both *in vitro* and *in vivo*)

   Mechanism: combines with antithrombin (natural anticoagulant factor) forming heparin-antithrombin complex which accelerates the inhibitory effect of antithrombin on activated clotting factors specially:

   - Factor IIa (Thrombin) - factor IXa - factor Xa.
2. Slight vasodilator effect ➔ canalization of thrombus.
3. Plasma-clearing effect by stimulating lipoprotein lipase enzyme.

Pharmacokinetics

- Immediate onset of action after IV injection and short duration (4-6 h).
- 80 % metabolized in the liver by heparinase enzyme.
- 20 % excreted unchanged via the kidney.
- Does not cross placenta & is not secreted in milk (high MW) ➔ can be used during pregnancy (if clearly indicated) or lactation.

Routes of Administration & Doses

- **IV bolus** (5,000 IU), followed by **IV infusion** (1,000 IU/h); guided by aPTT).
- **SC**: 5,000 IU (low dose of heparin) for prophylaxis, 2 hours preoperative and every 12 hours postoperative for 5-7 days.

Heparin should not be given by IMI as hematoma can occur.

Control of Therapy

- **aPTT** (activated partial thromboplastin time): should **Not > 2-2.5** normal value (normal value 30-35 seconds).

Adverse Effects

1. **H**emorrhage.
2. **H**air loss (alopecia).
3. **H**ematoma if given by IMI.
4. **H**ypersensitivity.
5. **H**yperkalemia (monitor K level if heparin is given > 7 days)
   2ry to aldosterone deficiency (due to inhibition of an enzyme necessary for aldosterone synthesis OR block of Ag-II receptors in suprarenal cortex)
6. Osteoporosis (on long term use, specially in pregnancy).
7. Heparin-induced thrombocytopenia (HIT): (regular platelet count is required):
   a) Early: mild due to direct effect on platelets.
   b) Late: severe due to immunoglobulin-induced platelet aggregation.

   ttt: Replace heparin by direct thrombin inhibitor or fondaparinux
8. Unpredictable pharmacokinetic & pharmacodynamic properties: (because it binds to plasma proteins, macrophages, platelets or endothelial cells)

Reversal of Heparin toxicity

- **Stop Heparin - Fresh blood transfusion**
- Give heparin **antidote**: **Protamine sulfate**
  - Highly basic with low MW carrying electropositive charge.
  - Neutralizes heparin (each **1** mg neutralizes ≈ **100** IU heparin, Not **exceed 50 mg** in any **10 min** period).
  - **Avoid overdose** → Has a slight anticoagulant effect.
  - Partially antagonizes Low-Molecular-Weight Heparins.
  - Does not antagonize fondaparinux.

2. Low-Molecular-Weight Heparins (LMWHs):

(Dalteparin - Enoxaparin -Tinzaparin)

- They are fractions of the standard heparin (unfractionated heparin) thus they have a low molecular weight.
- They are mostly given subcutaneously.
- Mainly renal excretion.

Mechanism of Action

- They bind to antithrombin increasing its inhibitory effect on factor $\mathbf{X_a}$ and to a lesser extent on thrombin (Factor II_a).

Advantages of LMWHs

1. Equal efficacy to unfractionated heparin.
2. Greater bioavailability from sc sites.
3. Long $t_{1/2}$ ➔ given subcutaneously once or twice/day.
4. Less thrombocytopenia & osteoporosis.
5. Less risk of bleeding.
6. No need for laboratory monitoring (predictable ph.kinetics & dynamics).

3. Indirect selective inhibitor of factor Xa: Fondaparinux

- Synthetic Pentasaccharide molecule, derivative of heparin
- Binds to antithrombin with ➔ efficient inactivation of factor Xa.
- Long $t_{1/2}$ ➔ given once daily sc**.**
- Low risk of HIT
- Used in venous thromboembolism & heparin - induced thrombocytopenia.
- Bleeding is the major adverse effect: not antagonized by protamine sulfate.
- Requires less monitoring than heparin (predictable ph.kinetics & dynamics)

II. Parenteral Direct Thrombin Inhibitors: (DTIs)

- Directly bind to thrombin independent of antithrombin → more inhibition of fibrin-bound thrombin.
- Given intravenously and Sc.
- Bleeding is the major adverse effect (NO antidote)
- Used in: - Percutaneous intervention (PCI) & Coronary angioplasty
  - Patients with HIT

Argatroban

- Preferred in patients with renal insufficiency (cleared hepatically not renally).

Bivalirudin (hirudin analogue)

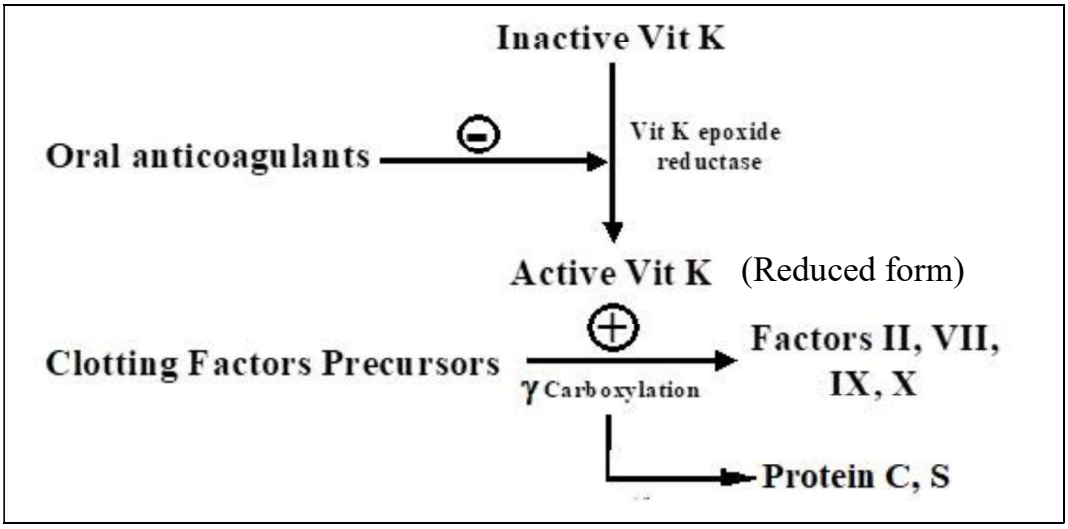
- Also inhibits platelet activation.

B. ORAL ANTICOAGULANTS

1-Warfarin:

Mechanism of Anticoagulant Action (effective only *in vivo*)

- Inhibition of vitamin K epoxide reductase enzyme → prevention of reactivation of vitamin K → interference with hepatic synthesis of vitamin K-dependent clotting factors (II, VII, IX, X).



Pharmacokinetics

- Well absorbed after oral administration.
- More than 99 % bound to plasma proteins.
- Metabolized by liver & excreted by kidney.
- Long duration of action. (Extensive plasma protein binding + $t_{1/2}$ 36 hrs)
- Crosses placenta **(Category D)**.
- Secreted in milk (negligible amounts → safe during lactation).

Dosage of Warfarin

- **Loading dose:** 5- 10 mg/day (followed by maintenance dose).
- **Maintenance dose**: 5-7 mg/day (according to INR).

Control of Therapy

- **PT** (**P**rothrombin **T**ime):

  Should be kept at 2-2.5 normal value (12-14 s).

- **INR (I**nternational **N**ormalized **R**atio = PT of patient/normal PT):

  Should be kept at 2-3.

Antidotes for oral anticoagulants

- Fresh frozen plasma.
- Vitamin K_1.

Adverse Effects

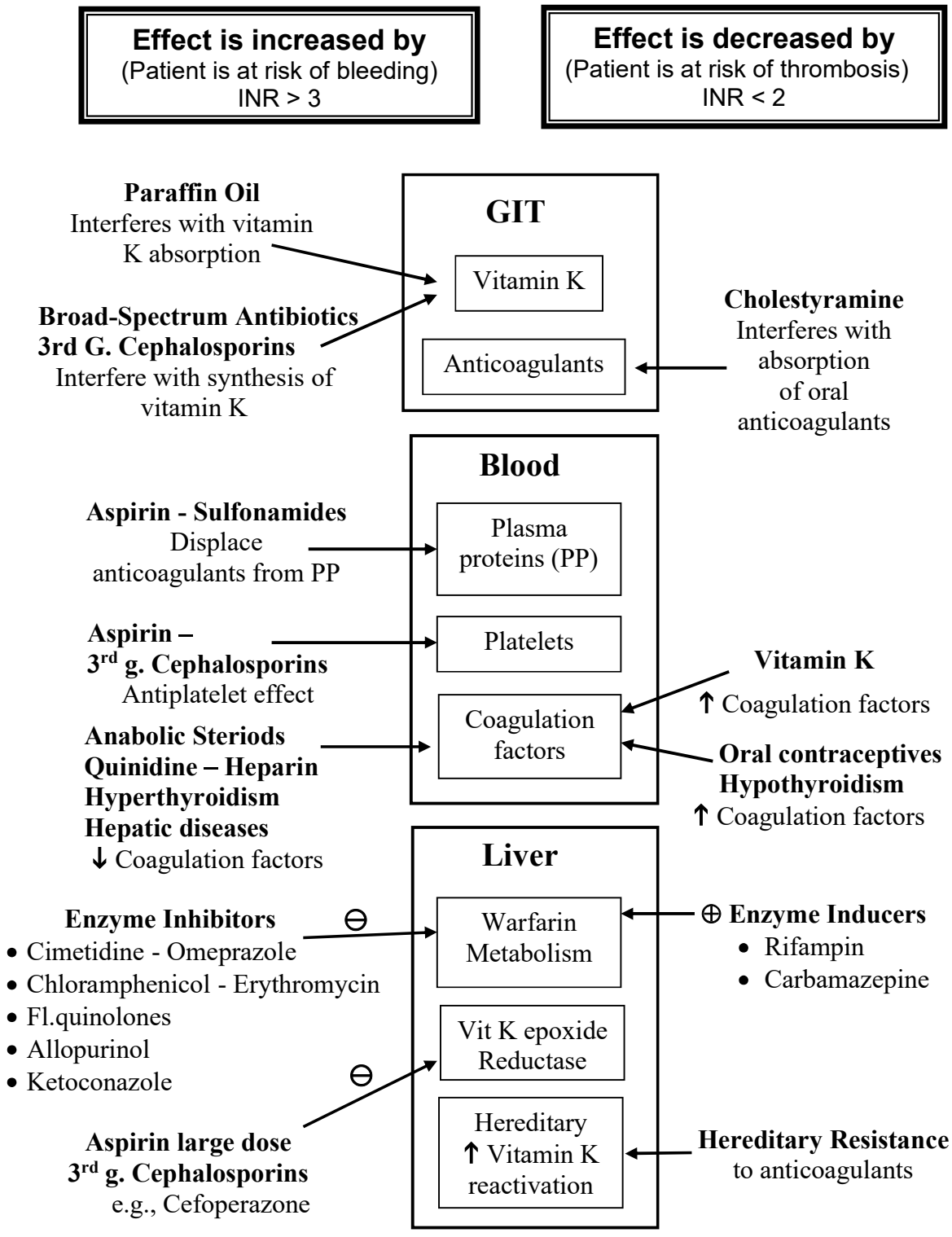
1. Hemorrhage.
2. Skin necrosis (especially in patients with protein C deficiency) [It is due to inhibitory effects of warfarin on synthesis of protein C. The latter is a natural anticoagulant whose level drops at a rate faster than that of the clotting factors ➔ transient hypercoagulation ➔ venular thrombosis ➔ skin necrosis.]
3. Teratogenic (avoid in 1st trimester): abnormal bone formation.
4. Hemorrhage in fetus (stop 2 weeks before labor).

Disadvantages

- Delayed onset (2-3 days are required for depletion of already formed coagulation factors + $t_{1/2}$ 36 hrs, so CSS is reached after 6 days) ➔ requires overlapping therapy with heparin (see anticoagulation protocol).
- Requires routine monitoring of coagulation.
- Narrow therapeutic index
- Drug interactions.
- Long duration of action after stoppage of administration (up to 6 days)

Drug Interactions with Oral Anticoagulants

Requiring Dose Adjustment



2. Newer Oral Anticoagulants (NOAC)

Rivaroxiban - Apixaban - Dabigatran

Advantages over warfarin

1. More rapid onset and offset.
2. No monitoring is required with less risk of bleeding.
3. Less drug interactions with CYP450 interacting drugs.

Comparison of Oral Anticoagulants

	Warfarin	Rivaroxaban	Dabigatran
Mechanism	• ↓ Hepatic synthesis of clotting factors **(II-VII-IX-X)**.	• Direct competitive reversible inhibitor of factor **Xa**	• Direct competitive reversible inhibitor of **Thrombin**
Onset	• 36-72 hours	• Within 30 min	• Within 30 min
Duration	• Up to 6 days	• 24 hours	• 24-36 hours
Monitoring	• INR	• No	• No
Antidote	• Vitamin K	• NONE	• Idarucizumab
Interactions	• Significant	• < warfarin	• < warfarin
Renal impairment	• No dose adjustment.	• Dose adjustment • Avoid if creatinine clearance <15ml/min	• Dose adjustment • Avoid if creatinine clearance <15ml/min
Pregnancy	• **Teratogenic**	• Unknown	• Unknown

N.B.

1. **Apixaban is similar to rivaroxaban with less risk of bleeding**.
2. **Dabigatran** is a prodrug with very low bioavailability". **Absorption** depends on acid environment → **decreased by proton pump inhibitors**.
3. Food increases bioavailability of rivaroxaban.
4. Bioavailability: dabigatran: 6.5%, rivaroxaban: 80%, warfarin: 100%.

Indications of Anticoagulants

Aim of Therapy (limits propagation & prevents formation of new thrombi)

1. Prophylaxis of venous thrombo-embolism (VTE) [deep venous thrombosis (DVT)/pulmonary embolism (PE)]: after knee or hip surgery.
2. Treatment of venous thrombo-embolism (VTE).
3. Stroke prevention in AF (atrial fibrillation) cases.
4. Arterial thrombosis: coronary, cerebral
5. Cardiac & vascular surgery
6. Hemodialysis .

Heparin

Contraindications of Anticoagulants

A. Increased risk of bleeding

1. Hemophilia, purpura.
2. Head injuries.
3. Intracranial hemorrhage.
4. Severe or uncontrolled hypertension.
5. During or sfter brain, spinal cord or eye surgery.
6. Threatenend abortion.
7. Active peptic ulcer.
8. Active TB.

B. Allergy

Protocol for anticoagulation

- **Heparin** (initially), followed by concomitant administration of **oral** anticoagulants for 2-3 days before stopping heparin (guided by INR).
- **Rivaroxaban** is approved as initial oral treatment of DVT

Anticoagulation in pregnancy

- Heparin (in 1st trimester) then switch to warfarin.
- Warfarin is stopped 2 weeks before labor & heparin is restarted, to be stopped 12 hours before labor induction.
- LMWHs are preferred to heparin → ↓ risk of osteoporosis (Vertebral compression fracture).

FIBRINOLYTICS (THROMBOLYTICS)

- Drugs that cause lysis of clot (thrombus). They are given intravenously.

Mechanism of Action

- Fibrinolytics are plasminogen activators. They activate plasminogen to plasmin which causes degradation of fibrin:

Plasminogen (natural plasma glycoprotein) —(Plasminogen activators)→ **plasmin** → **dissolves fibrin (clot)**

N.B.:

- Plasmin digests not only fibrin but also fibrinogen and factors V & VIII. So bleeding may occur if excess plasmin circulates in plasma.

The ideal fibrinolytic is that which activates plasminogen bound to fibrin (fibrin-specific) without activating free plasminogen in plasma.
So its effect is localized to clot → ↓ risk of bleeding.

Indications of Fibrinolytics

1. Acute myocardial infarction (most effective if given early within 6 hours).
2. Massive pulmonary embolism.
3. Thrombotic stroke
4. Acute peripheral arterial occlusion.
5. Deep venous thrombosis.
6. Obstructed arteriovenous shunt & occlusion of intravascular catheter.

Fibrinolytic therapy should be started as soon as possible after the onset of thrombosis or embolism (since they become resistant to lysis as they age).

Classification of Fibrinolytics

Fibrin-Nonspecific (1st generation)

A. Streptokinase (SK)

B. Urokinase (UK)

- **Source: SK**: cultures of β-hemolytic streptococci, and **UK**: cultures of human renal cells & urine
- **Non clot-selective**: activate both circulating & clot (fibrin)-bound plasminogen:

A. SK: acts indirectly forming a complex with plasminogen which then activates free plasminogen

Advantage: (cheapest & most widely used).

B. UK: directly activates plasminogen

Advantage: (non antigenic).

Disadvantages

- ↑ bleeding risk (non clot-selective)
- SK: Antigenic
- Given as IV infusion → loading dose followed by maintenance dose.

Fibrin-specific (2nd generation)

Recombinant Tissue Plasminogen Activators (tPA)

Alteplase – Tenecteplase Reteplase

- **Clot-selective**: greater affinity for activating clot (fibrin)-bound plasminogen than circulating plasminogen.

Advantages

- ↓ Bleeding risk (clot-selective).
- Nonantigenic.
- Tenecteplase is given as a single IV bolus dose (longer $t_{1/2}$).
- Reteplase: longer $t_{1/2}$

Adverse Effects

1. Bleeding (more with fibrin-nonspecific agents ➔ treated by stopping infusion, fresh blood & antifibrinolytics).
2. Antigenicity (fever, allergy & hypotension) with streptokinase (antibody formation following previous streptococcal infection) → start therapy with a large loading dose to neutralize antibodies.
3. Ischaemia-Reperfusion injury (IRI) [the paradoxical cellular injury, following restoration of blood flow after a period of ischemia. It occurs due to ↑ ROS (reactive oxygen species), Microvascular vasoconstriction and release of cytokines].
4. Microemboli (as the clot dissolves local thrombin increases → ↑ platelet aggregation & thrombosis).

Fibrinolytics should be followed by anticoagulants & antiplatelets

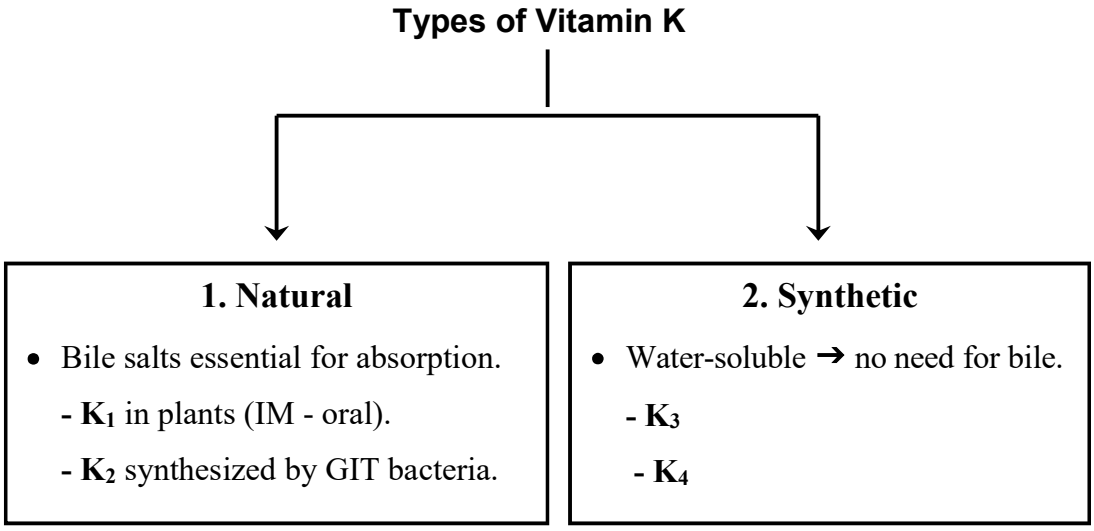
Contraindications

1. Recent surgery.
2. Gastrointestinal bleeding.
3. Hypertension.
4. Cancer.
5. Old age > 75y.

DRUGS USED IN BLEEDING DISORDERS

I. VITAMIN K

- Fat-soluble vitamin essential for hepatic synthesis of factors II, VII, IX and X.
- Deficiency of vitamin K leads to spontaneous hemorrhage.



Indications of Vitamin K

1. Overdose of anticoagulants & salicylates.
2. Hemorrhagic diseases in newborn.
3. Vitamin K deficiency (in obstructive jaundice or malabsorption syndrome).

Adverse Effects

- Rapid IV injection results in:
    1. Dyspnea.
    2. Chest pain.
    3. Flushing.

II. FIBRINOLYTIC INHIBITORS (ANTIPLASMIN)

1. Aminocaproic Acid

- Competitive inhibitor of plasminogen activators.

Uses

1. Bleeding due to fibrinolytics.
2. Adjunct therapy in hemophilia.
3. Bleeding states resulting from damage of tissues rich in plasminogen activators (e.g. after prostatic surgery, tonsillectomy).

Adverse Effects

- Hypotension.
- Abdominal discomfort.
- Intravascular thrombosis.

2. Tranexamic Acid

- Analog of aminocaproic acid that is more potent with fewer side effects.

3. Plasma Fractions

- Given when there is deficiency of one of the coagulation factors, e.g.:
    - Factor VIII given in hemophilia.
    - Factor IX.
    - Fibrinogen.

Cryoprecipitate

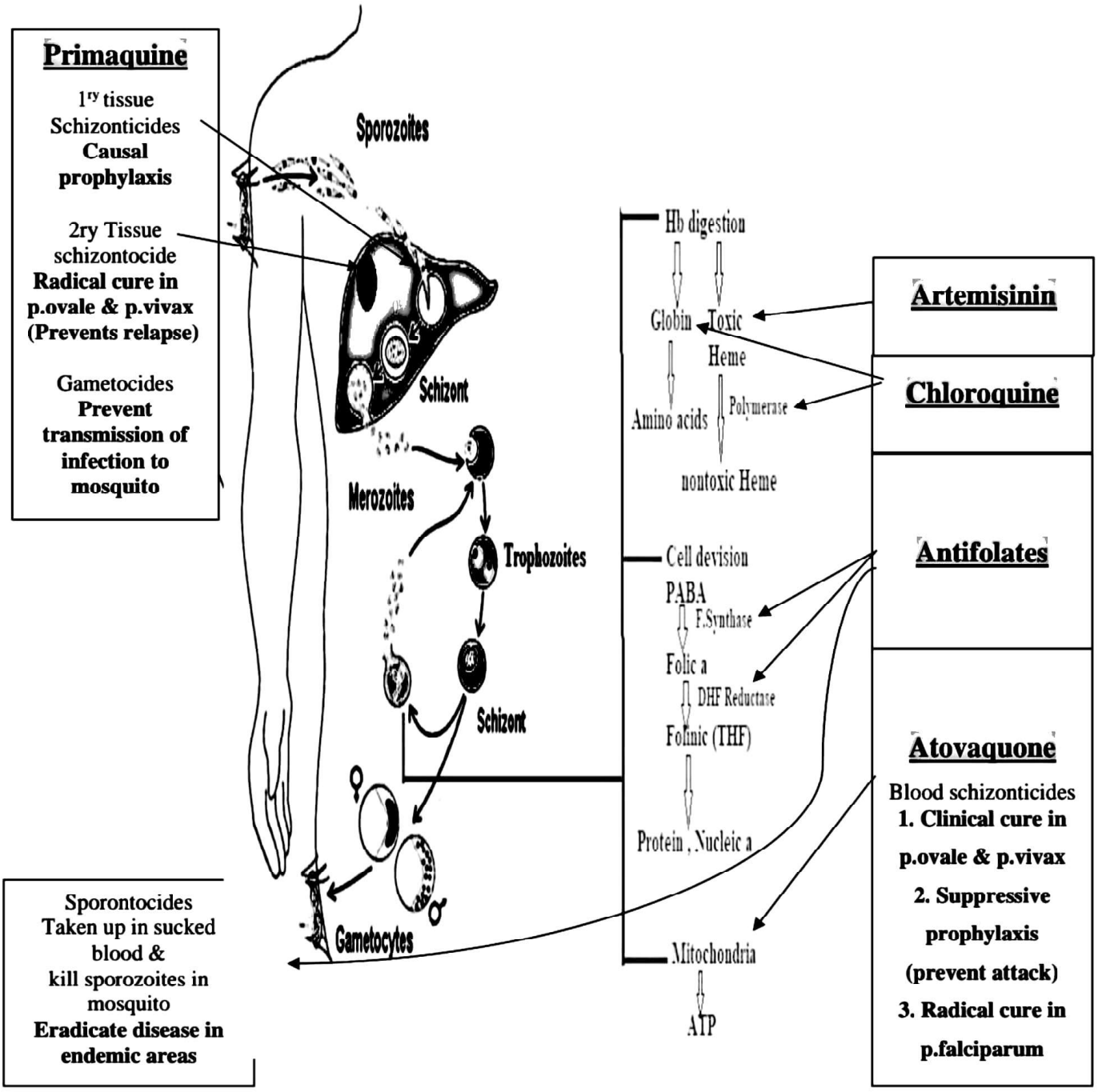
Plasma protein rich in factor VIII, von Willebrand factor & firbinogen.

DRUG THERAPY OF MALARIA

- Malaria is caused by 4 species of plasmodia (P): P. ovale, P. vivax, P. malarie & P. falciparum.

Life cycle of malaria

1. **Primary tissue phase (pre-erythrocytic)**.
   - Infected mosquito injects **sporozoites into victim's blood** which develop into **schizonts in liver cells** forming thousands of **merozoites**.
2. **Erythrocytic phase** (responsible for clinical picture)
   - Merozoites invade **RBCs** & develop into **trophozoites** which multiply and form more merozoites.
   - Infected RBCs rupture releasing merozoites → clinical attack.
   - Merozoites re-enter fresh RBCs to repeat the erythrocytic phase.
3. **Secondary tissue phase (exoerythrocytic) (in P.ovale & P.vivax only)**
   - Some parasites remain inactive in liver cells for months or years. Re-activation of **dormant forms (hypnozoites)** in **liver cells** → RELAPSE
4. **Gametocytes:** after several cycles, parasites in **RBCs** may develop into **male & female gametocytes** that are infectious to mosquitoes.
5. Mosquitos pick up gametocytes that develop into sporozoites & are stored in salivary glands.
6. Life cycle is repeated when infected mosquitoes inject sporozoites into the blood of a new victim.



Life cycle of malaria & Site of Action of Antimalarial Drugs

Drug therapy

Types of treatment:

1. Chemoprophylaxis: (Killing the parasite before multiplication inside RBCs)

- **Causal prophylaxis:** killing the parasite in the liver
- **Suppressive prophylaxis**: killing the parasite as soon as they reach the RBCs.

2. Clinical cure: (killing the parasite in the RBCs)

3. Radical cure: (clearing the hypnozoites from the liver to prevent relapse)

4. Prevention of transmission: (killing the gametocytes)

Problems

- **Chloroquine resistance**: Chloroquine is the mainstay of antimalarial therapy but resistance to drug (geographically distributed) is a major problem especially with P. falciparum (most dangerous → encephalopathy & renal failure).
- **Relapse:** Re-activation of dormant form in hepatic cells → relapses in P. ovale & vivax not in P. falciparum.

INDIVIDUAL DRUGS

A. 4-aminoquinolines

Chloroquine - Quinine - Mefloquine - Amodiaquine

1. Chloroquine

- Blood schizonticide.
- Moderately effective gametocidal in all species except falciparum.

Mechanism of action: highly concentrated in infected RBCs

- Inhibits parasite hemoglobin digestion → ↓ nutrient amino acids for parasite.
- Inhibits parasite heme polymerase → accumulation of toxic heme.

Therapeutic uses

1. Prophylaxis & treatment of chloroquine-sensitive malaria:

- Radical cure in p.falciparum & clinical cure in p.ovale & p.vivax (followed by primaquine to eradicate dormant form→ prevent relapse).

2. Amoebic hepatitis and amoebic liver abscess.

3. Rheumatoid arthritis (anti-inflammatory effect).

Adverse effects of chloroquine

1. GIT: Nausea-vomiting and diarrhea

2. C.V.S.: quinidine like action (hypotension & arrhythmias [↑ QT interval]).

3. CNS: Headache - tinnitus – dizziness

4. Eye: Corneal opacity - blurred vision and retinopathy.

5. Blood: Hemolytic Anemia in G6PD-deficient patients.

2. Quinine

- **Mechanism:** Same as chloroquine
- Used in treatment of chloroquine resistant falciparum but NOT in prophylaxis (too toxic).
- Weak antipyretic – weak muscle relaxant (used in muscle cramps).
- **Adverse effects:**
  1. GIT…..
  2. CVS….
  3. Cinchonism: CNS:….. + Eye → blurred vision and blindness.
  4. Black water fever & hemolysis (Allergic reaction to drug: marked hemolysis→ hemoglobinuria → black color of urine).
  5. Oxytocic on uterus→ abortion

3. Mefloquine

- **Mechanism:** Same as chloroquine
- More effective- longer acting - less toxic than Quinine
- **Uses:** Treatment & prophylaxis of chloroquine resistant falciparum.
- **Adverse effects:** GIT……, CVS….., CNS….

4. Amodiaquine:

- **Mechanism**: Same as chloroquine.
- **Uses:** Treatment & prophylaxis of chloroquine resistant falciparum.
- **Adverse effects:** Bone marrow suppression.

B-Artemisinin & derivatives

- Rapidly acting blood schizonticidal against all human malaria parasites.

Mechanism of action:

- Cleavage of the drug's endoperoxide bridge → free radicals.

Therapeutic uses

- Treatment of multidrug resistance P. falciparum.

Adverse effects: GIT…..**,** CVS…….

Derivatives: Oral, rectal, IM;

- Artemether
- Artesunate (also available IV)

C-Atovaquone

- Active against tissue and erythrocytic schizonts.

Mechanism of action:

- Inhibits mitochondrial electron transport, ATP & pyrimidine biosynthesis.

Therapeutic uses: oral

- Prevention & treatment of chloroquine resistant falciparum (plus proguanil).

Adverse effects: GIT…, CVS…, CNS… + liver toxicity.

D. Primaquine (8-aminoquinolines)

- Tissue schizonticide & gametocide (unknown mechanism of action).

Therapeutic uses:

1. Radical cure of relapsing malaria (tissue schizonticide given after a blood schizonticide to eradicate dormant form).
2. Terminal prophylaxis of relapsing malaria (given after leaving the endemic area to ensure that dormant forms are eradicated)
3. Prevents transmission of disease to mosquito (gametocide).

Adverse effects: GIT…, CNS…., in G6PDD… + Teratogenic

E. Antifolate Antimalarial drugs

Pyimethamine - Proguanil - Sulfadoxine.

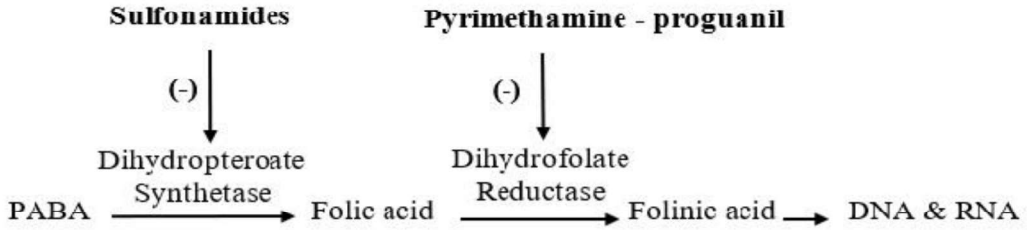
Fansidar (pyrimethamine + sulfadoxine)

- Blood schizonticides (mainly) – sporontocides.

Mechanism of action:

- **Inhibit folate pathway at 2 sequential steps →inhibit synthesis of DNA & RNA**

1. Sulfonamides inhibit synthesis of folate by competition with PABA.
2. Pyrimethamine & proguanil inhibit dihydrofolate reductase → inhibit conversion of folic to folinic acid → inhibit synthesis of DNA& RNA.



Therapeutic uses:

1. Treatment of chloroquine resistant falciparum :
   - Atovaquone + proguanil
   - Artesunate + (pyrimethamine + sulfadoxine) (fansidar)
2. Toxoplasmosis (pyrimethamine + sulfadiazine).

Side effects:

1. Hypersensitivity.
2. Megaloblastic anemia
3. Hemolytic anemia (in G6PDD).

N.B.: tetracycline & doxycycline are blood schizonticides (not used alone).

Treatment of Malaria

	Treatment	Prophylaxis
Chloroquine Sensitive	**Chloroquine** for 3 days	**Chloroquine** once/week: 1-2 weeks before travel, through travel, for 4 weeks after leaving endemic area
	+ **Primaquine** for 14 days (in vivax & ovale to prevent relapse)	
Chloroquine Resistant falciparum	• Atovaquone-Proguanil OR • Mefloquine • Quinine + doxycycline	• Atovaquone-Proguanil OR • Mefloquine • Doxycycline

IMMUNOMODULATORS

The Immune System:

- The immune system protects the body from invading pathogens & eliminates disease, while still capable of recognizing and toleratating "self" antigens.

Components of Immune System:

I. Innate (Natural):

- **Physical** → skin, mucus membrane (epithelial barrier)
- **Biochemical** → complement, lysozymes, epithelial natural antibodies.
- **Cellular** → macrophages, neutrophils.

II. Adaptive (Acquired): 2nd line defense if innate immune response is inadequate

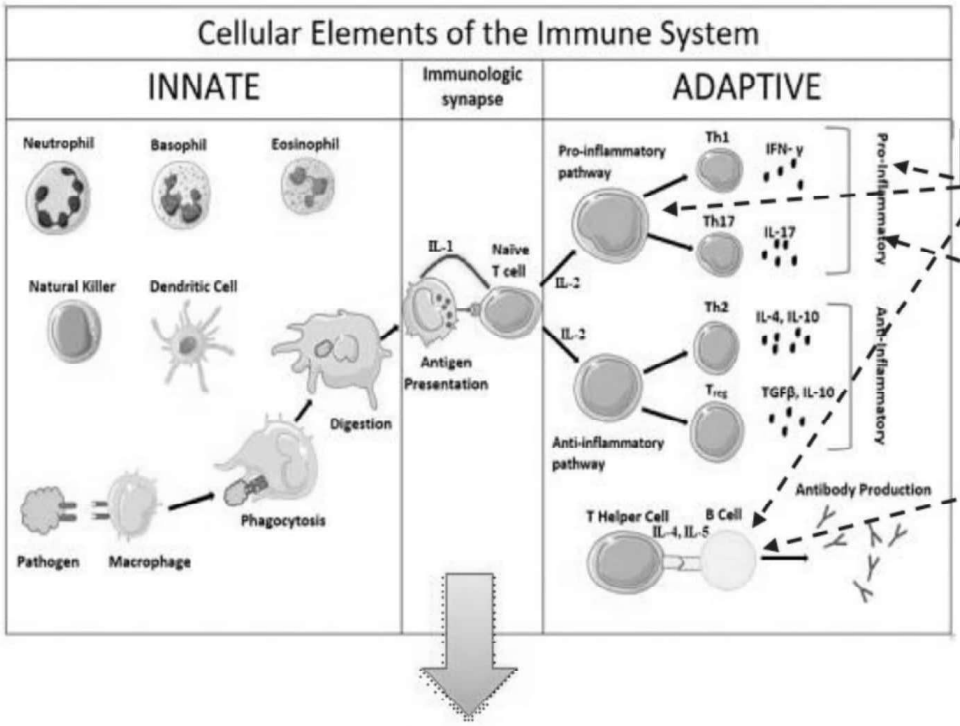
- **Humoral immunity**: → B-lymphocytes → Ig antibodies → eliminate extracellular microbes & toxins.
- **Cell Mediated immunity:** → T-lymphocytes (Kill bacteria, tumor cell & virus infected cell) → eliminate intracellular microbes.

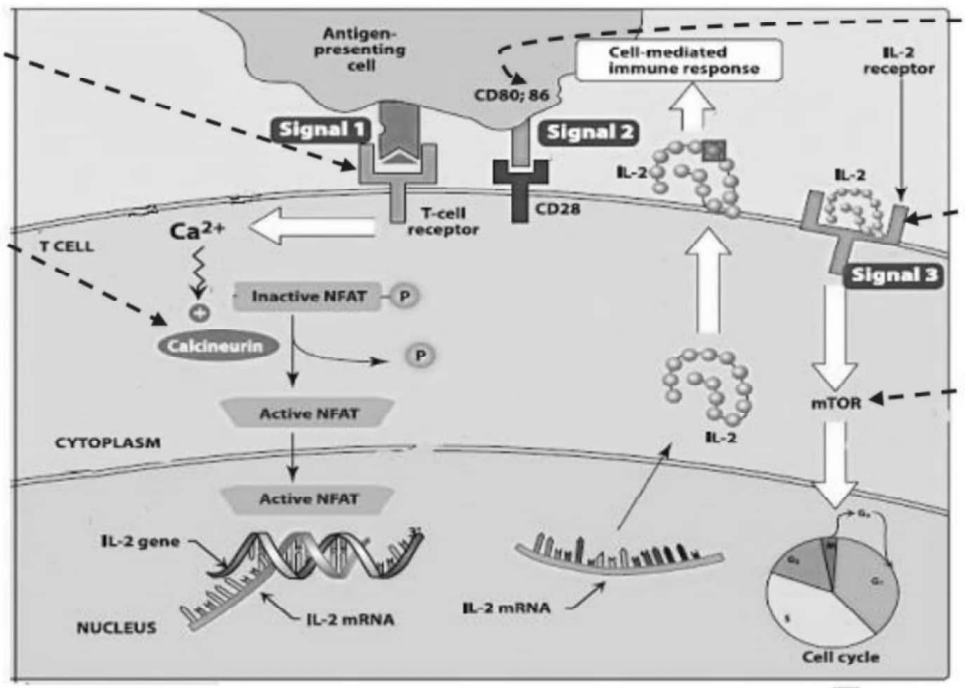
Major Steps in Immune Responses:

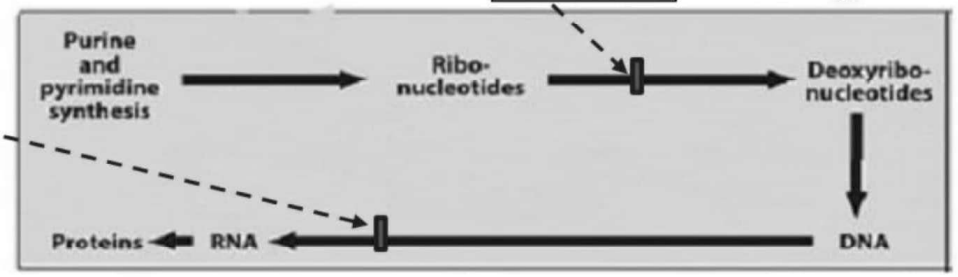
The immune activation cascade can be described as a **three-signal model**

1. **Signal 1:** Antigen-presenting cell (APC) → antigen presentation on its surface & IL-1 production → T-cell triggering at the CD3 receptor complex. [Signal 1 alone is insufficient for T-cell activation].
2. **Signal 2 (costimulation):** CD80 and CD86 on the surface of APCs → engage CD28 on T cells.

   activate the intracellular calcium-calcineurin pathway → activation of nuclear factor of activated T cells (NFAT) → ↑↑ the production of IL-2and other cytokines. [calcineurin is a protein – NFAT is a specific T-cell transcriptional factor]
3. **Signal 3:** IL-2 binds to the IL-2 receptor on the surface of other T cells → activation of the mammalian target of rapamycin (mTOR) → Lymphocyte proliferation & differentiation.







Corticosteroids

TNF binding Abs

B-cell receptor blockers

T-cell receptor blockers

APC receptor blockers

Calcineurin pathway inhibitors

IL-2 receptor blockers

mTOR signal inhibitors

Antifolate

Alkylating agents

Abnormal Immune Responses

I. Hypersensitivity:

- Immediate hypersensitivity (Type-I, Type-II, Type-III): usually Ig-mediated.
- Delayed hypersensitivity (Type IV): cell-mediated

II. Autoimmune diseases:

- Activation of self-reactive T and B lymphocytes → cell-mediated or humoral immune responses against self-antigens e.g. Rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis (MS), etc....

III. Immunodeficiency diseases:

- These are diseases resulting from inadequate function in the immune system → ↑ susceptibility to infections and prolonged duration & severity of disease.
- Immunodeficiency diseases may be either congenital or secondary to bacterial or viral infections (AIDS) or drug treatment.

Drugs Acting on the Immune System:

- They are used for treatment of abnormal immune responses.
- They are classified into: I. Immunosuppressants II. Immunostimulants

IMMUNOSUPPRESSANTS

I. Corticosteroids: methylprednisolone & dexamethasone.

Immunosuppressive mechanism:

1. Inhibition of T-cell function:↓ release of cytokines (interleukins and TNF-α).

2. Inhibition of B-cell function: ↓ antibodies production.

3. Inhibition of inflammatory process: ↓ cell adhesion, migration, chemotaxis, inflammatory mediators.

Immunosuppressive uses:

1. Organ transplant.
2. Autoimmune disease.

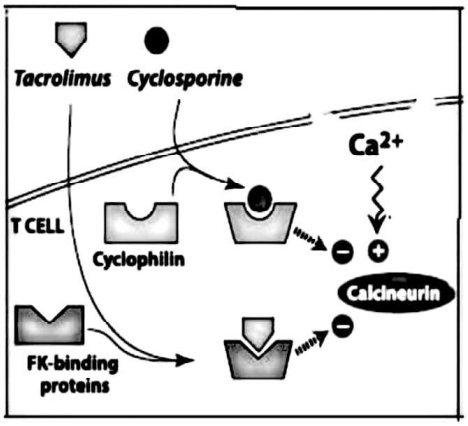
Adverse effects:

1. Increase risk of infections
2. Iatrogenic Cushing (Moon face, ↑ abdominal fat, Buffalo hump, thin arms & legs)
3. Hyperglycemia
4. salt and water retention 5. Osteoporosis 6. Cataract

II. Drugs acting on immunophilins:

A. Calcineurins inhibitors: Cyclosporine- tacrolimus

1- Cyclosporine (ciclosporin):



Mechanism of action:

- Binds to an immunophilin (cyclophilin) → a complex → inhibits calcineurin → ↓cytokines (e.g. IL-2) production by T lymphocytes.

Adverse Effects:

1. Nephrotoxicity (↑ with CYP450 inhibitors)
2. Hepatotoxicity
3. Hypertension 4. Hyperglycemia 5. Hyperkalemia 6. Gum Hypertrophy

Uses:

1. Organ & bone marrow transplantation.
2. Autoimmune diseases
3. Bronchial Asthma

2. Tacrolimus

Mechanism of action & adverse Effects: similar to cyclosporine (but binds to an immunophilin, FK-binding protein (FKBP).

Uses:

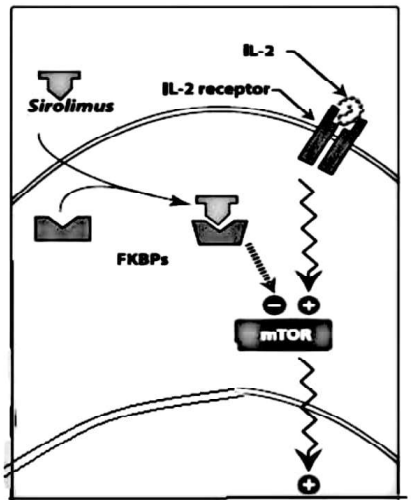
1. Organ transplantation. 2. Skin disorders (Atopic dermatitis - Psoriasis).

B. Proliferative (mTOR) signal inhibitors: Sirolimus

Mechanism of action:

- Binds to FKBP → a complex → blocks mTOR3 → ↓ cell proliferation & angiogenesis.

Adverse Effects:



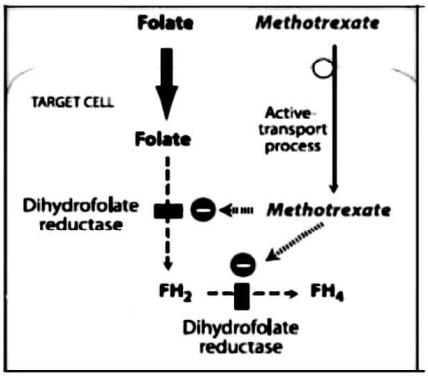
1. Bone marrow depression.
3. Hypertriglyceridemia.
4. Headache.
2. Hepatotoxic.

Uses:

1. Solid organ & bone marrow transplantation.
2. Dermatological disorders.
3. Sirolimus eluting stent: prevent restenosis by its antiproliferative effect.

IV. Cytostatic agents

- Cytotoxic agents inhibit cell division and used in the treatment of malignant diseases.
- In immunotherapy, they are used in smaller doses → inhibit the proliferation of both T cells and B cells (cytostatic).



A. Antifolate pathway: Methotrexate

Mechanism of action:

It inhibits dihydrofolate reductase (DHFR) enzyme → ↓ activation of folic acid to tetrahydrofolic acid → block purine and pyrimidine synthesis → inhibition of cell division (with greater effect on lymphocytes).

Clinical uses:

1. Cancer chemotherapy: effective for a number of cancers.
2. Autoimmune diseases

   [Folic acid 5 mg must be given 24h after methotrexate dose to compensate for folic acid deficiency and prevent bone marrow suppression].

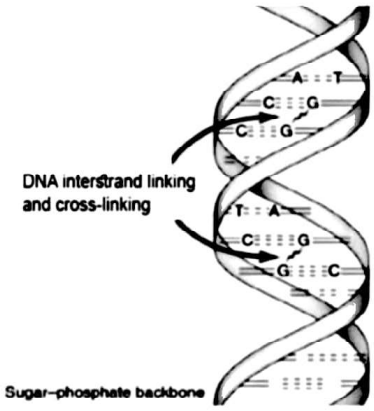
Adverse effects:

1. Hepatotoxicity is the most common (monitoring liver functions is essential)
2. General adverse effects of cytotoxic agents:
   - bone marrow suppression
   - Immunosuppression → ↑ infections.
   - GIT: vomiting, diarrhea and ulcers.
   - Hair loss.
   - Teratogenicity
   - Hyperuricaemia

<u>B. Alkylating agents:</u> Cyclophosphamide

Mechanism of action:

cross links DNA → inhibits cell replication → inhibits T cell & B cell function.



Uses:

1. Autoimmune diseases.
2. Cancer chemotherapy

Adverse Effects:

1. Hemorrhagic cystitis.

2. Adverse effects of cytotoxic drugs: e.g., bone marrow depression….

V. Monoclonal antibodies (mabs, nibs) and immunoglobulin-based agents:

1. APC receptor directed antibodies:

Abatacept: binds to APC receptors (CD80 & CD86)

2. T-cell receptor directed antibodies:

Muromonab-CD3: binding the T-cell receptor (CD3) → ↓ T-cell activation & proliferation.

3. IL-2 receptor directed antibodies:

Basiliximab: binds to the IL-2 receptor of T-cells (CD25).

In Rheumatoid Arthritis

4. B-cell receptor directed antibodies:

Rituximab: binds to the B-cell receptor (CD20) → ↓ B- cell activation & proliferation.

5. TNF binding antibodies:

Infliximab & adalimumab: bind to TNF-α → ↓ induction of IL-1 and IL-6 synthesis.

In Renal Transplant

IMMUNOSTIMULANTS

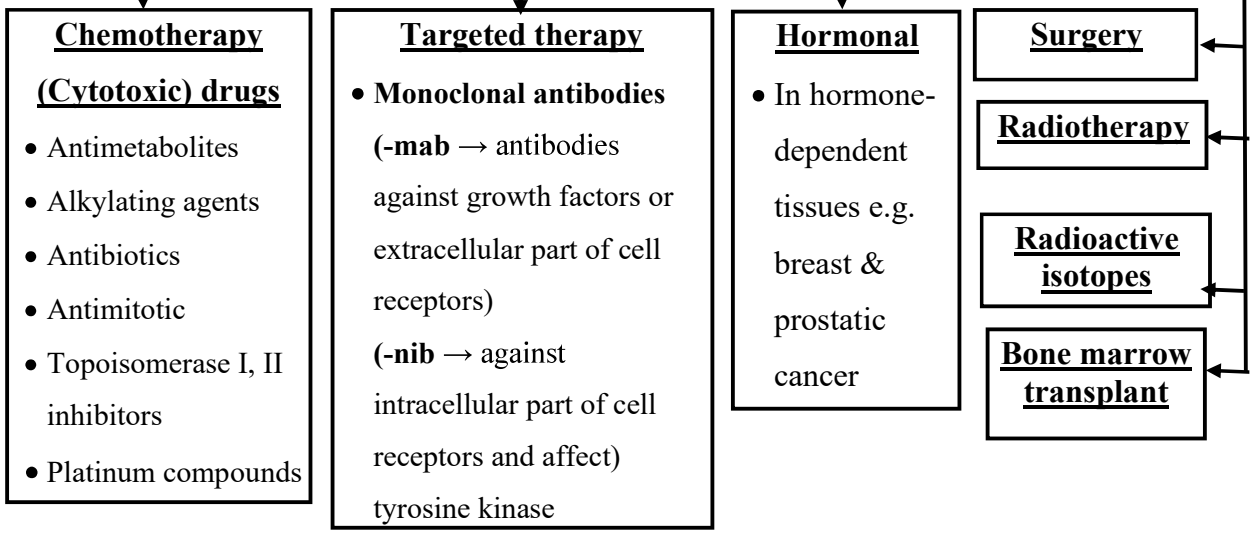
Types of Immunostimulants:

- Colony stimulating factors
- Interleukins
- Interferons
- Bacterial vaccines
- Viral vaccine

Drug	Mechanism	Indications
1. (GM-CSF) Granulocyte/macrophage colony stimulating factor	stimulate myelopoiesis in granulocyte-macrophage + megakaryocytic + erythroid pathways	- Neutropenia - Aplastic anemia, - after bone marrow transplantation (to stimulate stem cells).
2. (G-CSF) Granulocyte colony stimulating factor	stimulates maturation of immature neutrophils	- Neutropenia due to cancer chemotherapy
3. Aldesleukin (IL-2)	- T cell proliferation. - TH, NK cell activation	- Malignant Melanoma. - Renal cell carcinoma.
4. Oprelvekin (IL-11)	stimulate growth of megakaryocytes to form mature platelets	- Thrombocytopenia
5. Interferons	- Bind to specific cell membrane receptors → inhibition of viral penetration, replication & release. - ↑ macrophages activity - ↑ T cells Proliferation.	- **H**epatitis B & C. - **H**IV infection (AIDs). - **H**airy cell leukemia.

TREATMENT OF LEUKEMIA

Lines of treatment of the malignant tumors



Types of treatment of the malignant tumors:

1. **1ry therapy:** target the tumor itself e.g. surgical removal
2. **Adjuvant:** target the remnants of tumor i.e. after the 1ry, use cytotoxic drugs, hormonal, or radiation therapy
3. **Neoadjuvant:** target the tumor to decrease its size or vascularity i.e. before 1ry, use cytotoxic drugs, hormonal, or radiation therapy
4. **Palliative (supportive) therapy**: target the complications occurred by tumor and therapy

Cytotoxic drugs:

- In combination:
  - Advantages:

    1. Synergism: Each drug attacks tumor cells at different phases of growth cycle (sequential effect)

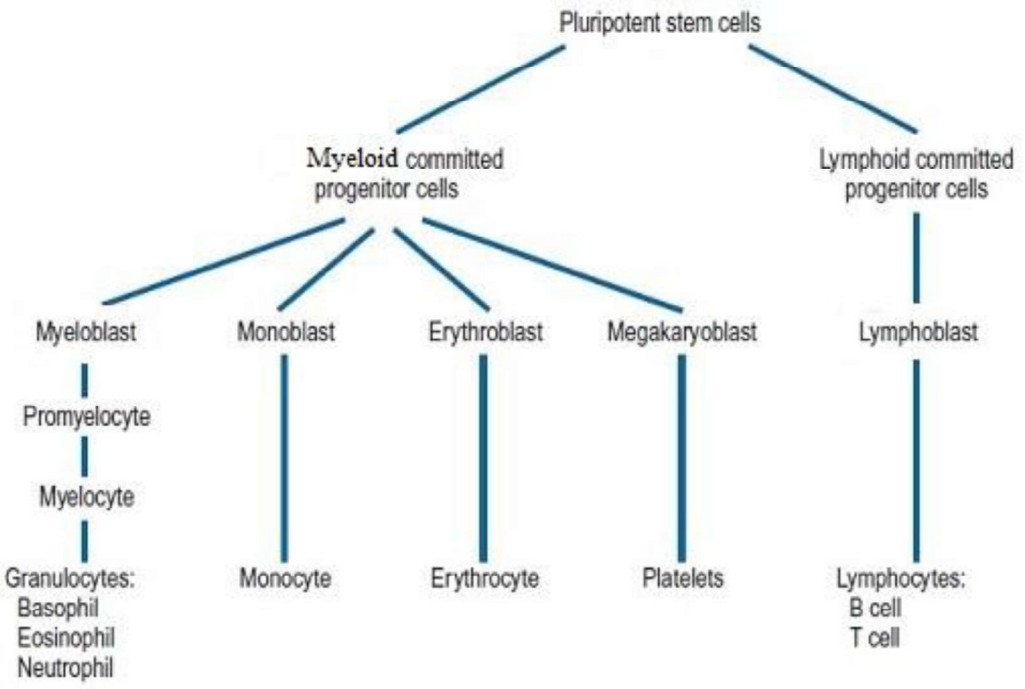
    2. Decrease incidence of resistance

    3. Decrease incidence of adverse effects due to use of small optimal doses.
  - Provided that drugs are None toxic to the same organ

- In cycles: act by % killing not absolute number killing
- Affect both cancer and normal cells:
  - Rapidly multiplying normal cells are more affected especially bone marrow cells → Neutropenia, thrombocytopenia and anemia

Leukemias:

- The normal process of haemopoiesis is altered → Accumulation of malignant cells → progressive impairment of the normal bone marrow function.



Types of Leukemias

A- Acute leukemias:

- > 20% of the cellular elements of the bone marrow are replaced with blast cells
- **ALL**: derived from the lymphoid series. The blasts may infiltrate lymph nodes and other tissues such as liver, spleen, testis and the meninges. or
- **AML:** derived from the myeloid series. The blasts tend to infiltrate skin, gums, liver and spleen

B- Chronic leukemias

- The normal bone marrow is replaced by a malignant clone of morphologically maturing haemopoietic cells (functionally deficient).
- **CLL:** is characterised by a clonal expansion of mature lymphocytes of B-cell origin → accumulate in - the peripheral blood → lymphocytosis
  - lymph nodes, liver and spleen.
- **CML**: is characterised by the predominance of maturing myeloid cells in blood, bone marrow, liver, spleen and other organs.

- the Philadelphia chromosome translocation (Ph) seen in over 90% of cases (a translocation of genetic material between the long arms of chromosome 22 and chromosome 9 → the apposition of the BCR gene (chromosome 22) and the ABL gene (chromosome 9) → novel BCR-ABL gene → encodes a protein with tyrosine kinase activity → uncontrolled growth characteristic of leukemic cells).

Treatment of Leukemias

I. Acute leukemia:

- **Induction of remission**: is the initial phase of treatment.
  - Remission is: 1- Bone marrow: < 5% blasts with normal maturation of all cell lines
    2. Peripheral blood:
    - Blasts 0% - Platelets > 100,000/uL
    - Hgb ≥ 11 g/dL - Neutrophils ≥ 1500/uL
  - Intensive combination cytotoxic drugs are given to achieve a complete remission (CR)
- **Consolidation (intensification) therapy**:
  - Aim: sustain CR (as minimal residual disease [MRD] will persist),
  - It comprises chemotherapy drugs and bone marrow transplantation.
- **CNS prophylaxis:**
  - Cranial irradiation + chemotherapy (intrathecal).
  - ALL: for all patients – AML: for patients at risk.
- **Maintenance therapy**
  - to sustain CR. - Milder than induction or consolidation chemotherapy.

II.Chronic leukemia

1. CML:

- The main aim: keeping patients asymptomatic by normalising the WBC, so take care of occurrence of - Acceleration (↑blast cells but not > 20%)
  - Blastic crisis (↑↑↑↑blast cells)
- Include: - Chemotherapy
  - Targeted therapy:
  - Palliative therapy e.g.
    - ➢ Surgery: Splenectomy for splenomegaly
    - ➢ Radiotherapy for localised painful lymphadenopathy or splenic complications.

2. CLL:

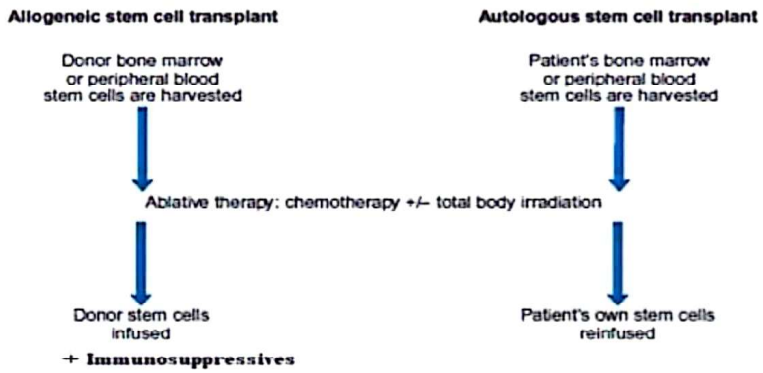
- Currently, there is no cure for CLL. Just wait and see
- Indications of treatment:
  - Rapidly ↑ WBC
  - ↑ lymphadenopathy
  - Systemic symptoms
  - Bone marrow failure
  - Autoimmune complications.
- Include: - Cytotoxic drugs and targeted therapy
  - Palliative therapy

Examples of drugs used for leukemia treatment:

- Chemotherapeutics: **Corticosteroids, Cyclophosphamide, Methotrexate**
- Targeted therapy: **Rituximab, imatinib** (it inhibits the abnormal tyrosine kinase product of the BCR-ABL fusion gene)

Bone marrow transplantation:

- Steps:
- Complications: **Infection** is almost unavoidable after bone marrow transplant



Common therapeutic problems in the leukemias:

1. Neutropenia: treatment by G-CSF or GM-CSF →
   - ↓ period of neutropenia → ↓ infection
   - Cycle of chemotherapy can be given on time
   - Risky in AML (need assessment of the case)
2. Thrombocytopenia: - treatment by platelets
   - In female: ↓ bleeding of menstruation (give contraceptive pills)
   - In expected bleeding ulcer: give ulcer protective drugs
3. Anemia: - treatment by blood transfusion
   - Erythropoietin Risky (need assessment of the case)
4. Tumour lysis syndrome
   - initiation of chemotherapy → lysis of cells → hyperuricaemia, hyperkalemia and hypocalcaemia → urate nephropathy
   - treatment: high fluid intake
     Allopurinol for hyperuricaemia
     Correct electrolytes disturbances
     Close monitoring of renal function, serum urate levels