DRUGS AFFECTING THE BLOOD

Haemostasis: is the arrest of blood loss from damaged vessels. It composed from two phases:

1- Platelets adhesion and activation.
2- Blood coagulation (fibrin formation).

Thrombosis: is pathological condition resulting from in appropriate activation of haemostasis mechanism forming thrombus. A portion from thrombus may break down and travel and floats on the blood forming or causing ischemia & infraction. Normally, the platelets circulate in the blood in the inactive form, since the endothelium layer (lining the blood vessels) secretes prostaglandin(PGI2) which when bind to it's receptor on platelets membrane . it's stimulating synthesis of CAMP which is inhibited release of platelet granules containing aggregating factors(ADP((adenosine diphosphate)) , serotonin & others).

The platelets membrane contain a variety of receptors that responding to different physiological and chemical stimuli. Some of these stimuli classified as platelet activating factors that promotes platelets aggregation and others as inhibitors to platelet aggregation. When vascular system exposed to physical trauma like cut or puncture, these initiate a series of interaction between endothelial platelets and coagulation factors, this cascade of steps results in the clot formation (plaque). This process requires platelet activation → aggregation → fibrin formation.

Platelet aggregation: The damaged endothelial layers secrete less amount of PGI2 so the CAMP is ↓ that's activating release of platelet granules containing aggregate factors like serotonin and ADP in a process called platelet release reaction and the platelet in this step said to be activated.

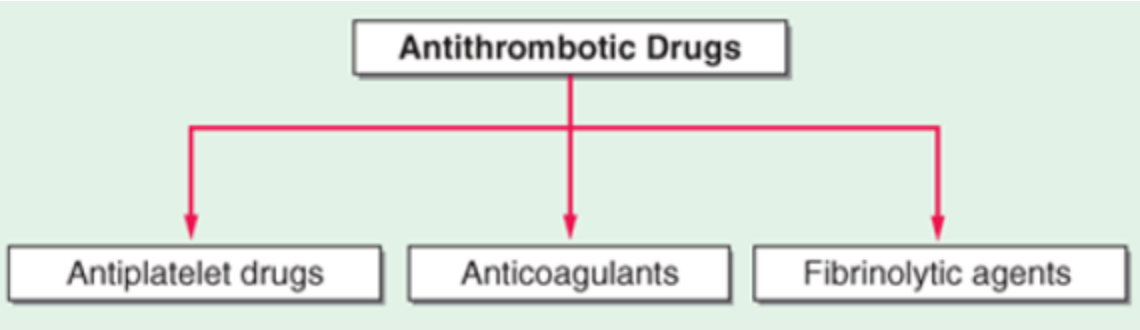
The mechanism includes:

Within seconds of injury, the platelets moved toward the subendothelial layer & adhere to collagen Layer& started to secrete ADP & serotonin and then aggregation of platelet occur.

Thromboxane A2 formation: the platelet activation also includes the increase of phospholipase A2 enzyme which is liberating arachidonic acid (AA) from phospholipid of platelet membrane. The AA in the presence of cyclooxygenase (COX) enzyme**,** so the thromboxane A2 (TXA2) produce further activation of aggregation process.

Blood coagulation: the coagulation process includes activation of intrinsic & extrinsic pathways. The coagulation results in clot formation, this fibrin when adhere to blood vessel wall called thrombus while when circulates with the blood, it's called embolus (both are danger for life).

Inhibitor of platelet aggregation: Antiplatelet Drugs



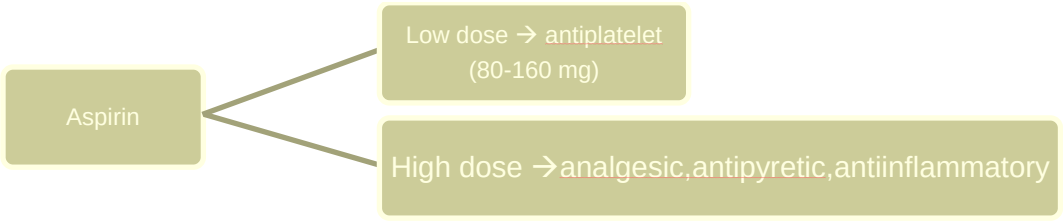
Platelet aggregation inhibitors decrease the formation of a platelet-rich clot or decrease the action of chemical signals that promote platelet aggregation. The platelet aggregation inhibitors inhibit cyclooxygenase-1 (COX-1) or block GP IIb/IIIa or ADP receptors, thereby interfering with the signals that promote platelet aggregation. Because these agents have different mechanisms of actions, synergistic or additive effects may be achieved when agents from different classes are combined. These agents are beneficial in the prevention and treatment of occlusive cardiovascular diseases, in the maintenance of vascular grafts and arterial patency, and as adjuncts to thrombin inhibitors or thrombolytic therapy in MI.

1- Aspirin (Acetylsalicylic Acid): TXA2 inhibitors –(non selective COX inhibitor)

Aspirin inhibits thromboxane A2 synthesis by acetylation of a serine residue on the active site of COX-1, thereby irreversibly inactivating the enzyme. Other salicylates and non-steroidal anti-inflammatory drugs also inhibit cyclooxygenase but have a shorter duration of inhibitory action because they cannot acetylate cyclooxygenase; that is, their action is reversible. The inhibitory effect is rapid and aspirin-induced suppression of Thromboxane A2 and the resulting suppression of platelet aggregation last for the life of the platelet, which is approximately 7 to 10 days. Repeated administration of aspirin has a cumulative effect on the function of platelets. Aspirin is the only antiplatelet agent that irreversibly inhibits platelet function.

Complete inactivation of platelet COX-1 is achieved with a daily aspirin dose of 75 mg.

- Note: Maximally effective at doses of 50-320 mg/day. Higher doses do not improve efficacy, potentially less efficacious because of inhibition of prostacyclin production.



Therapeutic use: *Aspirin* is used in the prophylactic treatment of transient cerebral ischemia, to reduce the incidence of recurrent MI, and to decrease mortality in the setting of primary and secondary prevention of MI. Also used in unstable angina, TIA-stroke prevention. Aspirin used as analgesic, antipyretic & anti-inflammatory.

Adverse effects: Angioedema, bleeding, bronchospasm, GI disturbances, Reye syndrome, peptic ulcers.

Note: Non-steroidal anti-inflammatory drugs, such as ibuprofen, inhibit COX-1 by transiently competing at the catalytic site. Ibuprofen, if taken within the 2 hours prior to aspirin, can obstruct the access of aspirin to the serine residue and, thereby, antagonize platelet inhibition by aspirin. Therefore, immediate release aspirin should be taken at least 60 minutes before or at least 8 hours after ibuprofen. Although celecoxib (a selective COX-2 inhibitor) does not interfere with the antiaggregation activity of aspirin.

2- Platelet ADP Receptor Antagonists (Thienopyridines)

Ticlopidine, clopidogrel, prasugrel, and ticagrelor are P2Y12 ADP receptor inhibitors that also block platelet aggregation but by a mechanism different from that of aspirin.

Ticagrelor binds to the P2Y12 ADP receptor in a reversible manner. The other agents bind irreversibly. The maximum inhibition of platelet aggregation is achieved in 1 to 3 hours with *ticagrelor*, 2 to 4 hours with *prasugrel*, 3 to 4 days with *ticlopidine*, and 3 to 5 days with *clopidogrel.*

Therapeutic use: *Clopidogrel* is approved for prevention of atherosclerotic events in patients with a recent MI or stroke and in those with established peripheral arterial disease. Ticlopidine is similar in structure to clopidogrel. It is indicated for the prevention of transient ischemic attacks (TIA) and strokes in patients with a priorcerebral thrombotic event. They are also used in aspirin-intolerant patients because of adverse side effects.

Pharmacokinetic: Ticlopidine, clopidogrel, prasugrel are prodrugs while ticagrelor is not prodrug. . Food interferes with the absorption of ticlopidine but not with the other agents. After oral ingestion, the drugs are extensively bound to plasma proteins. Because these drugs can inhibit CYP450, they may interfere with the metabolism of other drugs such as phenytoin, warfarin, fluvastatin & tamoxifen if taken concomitantly, indeed, phenytoin toxicity has been reported when taken with ticlopidene.

Adverse effects: Ticlopidine is associated with severe hematologic reactions that limit its use, such as agranulocytosis, thrombotic thrombocytopenic purpura (TTP), and aplastic anemia. Clopidogrel causes fewer adverse reactions, and the incidence of neutropenia is lower. However, TTP has been reported as an adverse effect for both clopidogrel and prasugrel (but not for ticagrelor).

3- Phosphdiesterase III inhibitors:

Dipyridamole is a vasodilator that also inhibits platelet function by inhibiting adenosine uptake and cGMP phosphodiesterase activity. Dipyridamole by itself has little or no beneficial effect. Therefore, therapeutic use of this agent is primarily in combination with aspirin to prevent cerebrovascular ischemia. It may also be used in combination with warfarin for primary prophylaxis of thromboemboli in patients with prosthetic heart valves. Dipyridamole commonly causes headache and can lead to orthostatic hypotension (especially if administered IV).

Cilostazol is a newer phosphodiesterase inhibitor that promotes vasodilation and inhibition of platelet aggregation. Cilostazol is used primarily to treat intermittent claudication. Side effects (diarrhea, abnormal stools, dyspepsia, and abdominal pain) are the most common adverse effects observed with cilostazol.

4- Glycoprotein IIb/IIIa inhibitors: Block final step in platelet aggregation induced by any agonist Abciximab, Eptifibatide, Tirofiban.

Abciximab is a monoclonal antibody that reversibly inhibits the binding of fibrin and other ligands to the platelet **glycoprotein IIb/IIIa receptor**, a cell surface protein involved in platelet cross-linking. Eptifibatide and tirofiban also reversibly block the glycoprotein IIb/IIIa receptor.

Therapeutic use: These agents are given intravenously, along with *heparin* and *aspirin*, as an adjunct to PCI for the prevention of cardiac ischemic complications.

The major toxicities of the glycoprotein IIb/IIIa receptor-blocking drugs are bleeding and, with chronic use, thrombocytopenia.

Anticoagulant drugs: Anticoagulants inhibit the formation of fibrin clots. Three major types of anticoagulants are available: heparin and related products, which must be used parenterally; direct thrombin and factor X inhibitors, which are used parenterally or orally; and the orally active coumarin derivatives (e.g. warfarin).

1- **Heparin** is a large sulfated polysaccharide polymer obtained from animal sources. With an average molecular weight of 15,000–20,000 Da. Heparin is highly acidic and can be neutralized by basic molecules. Low-molecular-weight (LMW) fractions of heparin (e.g.**enoxaparin, dalteparin and tinzaparin**) have molecular weights of 2000‑6000 Da. LMW heparins have greater bioavailability and longer durations of action than unfractionated heparin; thus, doses can be given less frequently (eg, once or twice aday). **Fondaparinux** is a small synthetic drug that contains the biologically active pentasaccharide present in unfractionated and LMW heparins. It is administered subcutaneously once daily. Heparin dosage determined by monitoring aPTT.(The aPTT is the standard test used to monitor the extent of anticoagulation with *heparin*)

Mechanism and effects:

Unfractionated heparin binds to endogenous antithrombin III (ATIII) .The heparin–ATIII complex combines with and irreversibly inactivates thrombin and several other factors, particularly factor Xa. In the presence of heparin, ATIII proteolyzes thrombin and factor Xa approximately 1000-fold faster than in its absence. Because it acts on preformed blood components, heparin provides anticoagulation immediately after administration. The action of heparin is monitored with the **activated partial thromboplastin time** (**aPTT**) laboratory test. LMW heparins and fondaparinux, like unfractionated heparin, bind ATIII. These complexes have the same inhibitory effect on factor Xa as the unfractionated heparin‑ATIII complex. However, the short-chain heparin‑ATIII and fondaparinux‑ATIII complexes provide a more selective action because they fail to affect thrombin. The aPTT test does not reliably measure the anticoagulant effect of the LMW heparins and fondaparinux; this is a potential problem, especially in renal failure, in which their clearance may be decreased.

Clinical use—Because of its rapid effect, heparin is used when anticoagulation is needed immediately (eg, when starting therapy). Common uses include treatment of DVT, pulmonary embolism, and acute myocardial infarction. Heparin is used in combination with thrombolytic for revascularization and in combination with glycoprotein IIb/IIIa inhibitors during angioplasty and placement of coronary stents. Because it does not cross the placental barrier, heparin is the drug of choice when an anticoagulant must be used in pregnancy. LMW heparins and fondaparinux have similar clinical applications. Also the drug is used in extracorporeal devices (for example, dialysis machines) to prevent thrombosis.

Pharmacokinetics: Heparin must be administered subcutaneously or intravenously, because the drug does not readily cross membranes, The *LMWHs* are administered subcutaneously. The anticoagulant effect with *heparin* occurs within minutes of IV administration (or 1 to 2 hours after subcutaneous injection), while I.M administration is contraindicated because of hematoma formation. The maximum anti–factor Xa activity of the *LMWHs* occurs about 4 hours after subcutaneous injection. The plasma levels and pharmacokinetics of LMWHs are more predictable compared with heparin. The half-life of *heparin* is approximately 1.5 hours, whereas the half-life of the *LMWHs* is longer than that of heparin, ranging from 3 to 12 hours. Renal insufficiency prolongs the half-life of LMWHs. Therefore, the dose of LMWHs should be reduced in patients with renal impairment.

Adverse effects:

- **Allergic and anaphylactic manifestations**
- **Bleeding (1-33%)-antidote- Protamine sulphate**
- **Heparin induced thrombocytopenia. (More than 25%)**
- **Alopecia**
- **Osteoporosis(with prolong used of unfractionated heparin but less with LMWHs)**
- **Hyperkalemia**

Heparin and LMWHs are contraindicated in patients who have hypersensitivity to heparin, bleeding disorders, alcoholism, or who have had recent surgery of the brain, eye, or spinal cord.

2- Direct Thrombin Inhibitors:

Chemistry and pharmacokinetics: Lepirudin is the recombinant form of the leech protein hirudin, while desirudin and bivalirudin are modified forms of hirudin. Argatroban is a small molecule with a short half-life. All 4 drugs are administered parenterally. Dabigatran is an orally active direct thrombin inhibitor.

Mechanism and effects: these drugs bind simultaneously to the active site of thrombin and to thrombin substrates. Argatroban binds solely to the thrombin-active site. Unlike the heparins, these drugs inhibit both soluble thrombin and the thrombin enmeshed within developing clots. Bivalirudin also inhibits platelet activation.

Clinical use: Direct thrombin inhibitors are used as alternatives to heparin primarily in patients with heparin-induced thrombocytopenia. Bivalirudin also is used in combination with aspirin during percutaneous coronary angioplasty. Like unfractionated heparin, the action of these drugs is monitored with the aPTT laboratory test.

Toxicity: bleeding (No reversal agents exist). Prolonged infusion of lepirudin can induce antibodies that form a complex with lepirudin and prolong its action, and it can induce anaphylactic reactions.

3- Warfarin and Other Coumarin Anticoagulants:

Chemistry and pharmacokinetics—Warfarin and other coumarin anticoagulants are small, lipid-soluble molecules that are readily absorbed after oral administration. The mean half-life of *warfarin* is approximately 40 hours, but this value is highly variable among individuals. Warfarin is highly bound to plasma proteins (>99%), and its elimination depends on metabolism by cytochrome P450 enzymes.

Mechanism and effects—

Warfarin and other coumarins interfere with the normal post-translational modification of clotting factors in the liver, a process that depends on an adequate supply of reduced vitamin K. The drugs inhibit vitamin K epoxide reductase (VKOR), which normally converts vitamin K epoxide to reduced vitamin K. The vitamin K-dependent factors include thrombin and factors VII, IX, and X. Because the clotting factors have half-lives of 8–60 hrs in the plasma, an anticoagulant effect is observed only after sufficient time has passed for elimination of the normal preformed factors. The action of warfarin can be reversed with vitamin K, but recovery requires the synthesis of new normal clotting factors and is, therefore, slow (6–24 hrs). More rapid reversal can be achieved by transfusion with fresh or frozen plasma that contains normal clotting factors. The effect of warfarin is monitored by the prothrombin time (PT) test.

Clinical use—*:* Warfarin is used in the prevention and treatment of DVT and PE, stroke prevention, stroke prevention in the setting of atrial fibrillation and/or prosthetic heart valves, protein C and S deficiency, and antiphospholipid syndrome. It is also used for prevention of venous thromboembolism during orthopedic or gynecologic surgery.

Toxicity— the principal adverse effect of *warfarin* is hemorrhage, therefore, it is important to frequently monitor the INR and adjust the dose of *warfarin*. Minor bleeding may be treated by withdrawal of the drug or administration of oral *vitamin K,* but severe bleeding may require greater doses of *vitamin K* given intravenously. Skin lesions and necrosis are rare complications of *warfarin* therapy. *Warfarin* is teratogenic and should never be used during pregnancy. If anticoagulant therapy is needed during pregnancy, *heparin* or *LMWH* may be administered. Because warfarin has a narrow therapeutic window and it is affected by hepatic enzyme inducer & inhibitor and drugs, CytochromeP450-inducing drugs (eg, carbamazepine, phenytoin, rifampin, barbiturates, dicloxacillin, chronic alcohol ingestion) increase warfarin's clearance and reduce the anticoagulant effect of a given dose. Cytochrome P450 inhibitors (eg, acute alcohol intoxication, fluconazole, metronidazole, amiodarone, selective serotonin reuptake inhibitors, cimetidine) reduce warfarin's clearance and increase the anticoagulant effect of a given dose.

Property	Heparins	Warfarin
Structure	Large acidic polysaccharide polymers	Small lipid-soluble molecule
Route of administration	Parenteral	Oral
Site of action	Blood	Liver
Onset of action	Rapid (minutes)	Slow (days); limited by half-lives of preexisting normal factors
Mechanism of action	Activates antithrombin III, which proteolyzes coagulation factors including thrombin and factor Xa	Impairs post-translational modification of factors II, VII, IX and X
Monitoring	aPTT for unfractionated heparin but not LMW heparins	Prothrombin time
Antidote	Protamine for unfractionated heparin; protamine reversal of LMW heparins is incomplete	Vitamin K_1, plasma, prothrombin complex concentrates
Use	Mostly acute, over days	Chronic, over weeks to months
Use in pregnancy	Yes	No

THROMBOLYTIC (FIBRNINOLYTIC) AGENTS:

Acute thromboembolic disease in selected patients may be treated by the administration of thrombolytic (fibrinolytic) agents that activate the conversion of plasminogen to plasmin, a serine protease that hydrolyzes fibrin and, thus, dissolves clots, so it must be given early as possible (3-12 hrs) from thrombosis because the clot with time become more resistant for lysis. Fibrinolytic drugs may lyse both normal and pathologic thrombi.

The thrombolytic drugs used most commonly are either (Fibrin specific) tissue plasminogen activator (t-PA; eg, alteplase, tenecteplase, and reteplase) that prepared by gene technology or Non-fibrin specific (streptokinase, Anistreplase& Urokinase). All are given intravenously.

Fibrin-nonspecific agents: binds equally to circulating and non-circulating plasminogen. produces breakdown of clot (local fibrinolysis) and circulating plasminogen & fibrinogen thus cause an unwanted (systemic fibrinolysis) leading to bleeding.

Fibrin-specific agents: are tissue plaminogen activators, selective in action (clot-specific fibrin), binds preferentially to plasminogen at the fibrin surface (non-circulating) rather than circulating plasminogen in blood. Risk of bleeding is less than non-specific agents.

Mechanism of Action

The thrombolytic agents act either directly or indirectly to convert plasminogen to plasmin, which, in turn, cleaves fibrin, thus lysing thrombi. Clot dissolution and reperfusion occur with a higher frequency when therapy is initiated early after clot formation because clots become more resistant to lysis as they age. Unfortunately, increased local thrombi may occur as the clot dissolves, leading to enhanced platelet aggregation and thrombosis. Strategies to prevent this include administration of antiplatelet drugs, such as aspirin, or antithrombotics such as heparin.

Alteplase is normal human plasminogen activator. It is contraindicated in patient with history of gentamicin hypersensitivity. *Alteplase* is approved for the treatment of MI, massive PE, and acute ischemic stroke. **Reteplase** is a mutated form of human t-PA, It has longer duration than alteplase (15 min.) with similar effects but a slightly faster onset of action..**Tenecteplase** is another mutated form of t-PA. It is more fibrin-specific & longer duration than alteplase. *Reteplase* and *tenecteplase* are approved only for use in acute MI, although *reteplase* may be used off-label in DVT and massive PE.

Streptokinase—Streptokinase is obtained from bacterial cultures. Unlike the forms of t-PA, streptokinase does not show selectivity for fibrin-bound plasminogen. It forms an active one-to-one complex with plasminogen. This enzymatically active complex converts uncomplexed plasminogen to the active enzyme plasmin. T 1/2 = less than 20 minutes. Not used in patients with: Recent streptococcal infections or previous administration of the drug.

Urokinase is produced naturally in the body by the kidneys. Therapeutic *urokinase* is isolated from cultures of human kidney cells and has low antigenicity.

Anistreplase (APSAC): It is a *prodrug*, de-acylated in circulation into the active plasminogen-streptokinase complex.$T_{1/2}$ is 70-120 min.It has longer duration of action than Streptokinase.

Clinical Use: The major application of the thrombolytic agents is as an alternative to percutaneous coronary angioplasty in the emergency treatment of coronary artery thrombosis. Under ideal conditions (ie, treatment within 6 h), these agents can promptly recanalize the occluded coronary vessel. Very prompt use (ie, within 3 h of the first symptoms) of t-PA in patients with ischemic stroke is associated with a significantly better clinical outcome. Cerebral hemorrhage must be positively ruled out before such use. The thrombolytic agents are also used in cases of severe pulmonary embolism.

Toxicity

The thrombolytic agents do not distinguish between the fibrin of an unwanted thrombus and the fibrin of a beneficial hemostatic plug. Thus, hemorrhage is a major side effect. For example, a previously unsuspected lesion, such as a gastric ulcer, may hemorrhage following injection of a thrombolytic agent. Streptokinase, a bacterial protein, can evoke the production of antibodies

((antigenicity)) that cause it to lose its effectiveness or induce severe allergic reactions on subsequent therapy. These drugs are contraindicated in pregnancy, and in patients with healing wounds, a history of cerebrovascular accident, brain tumor, head trauma, intracranial bleeding, and metastatic cancer. ***Alteplase*** may cause orolingual angioedema, and there may be an increased risk of this effect when combined with angiotensin-converting enzyme (ACE) inhibitors.

DRUGS USED IN BLEEDING DISORDERS:

Bleeding problems may have their origin in naturally occurring pathologic conditions, such as hemophilia, or as a result of fibrinolytic states that may arise after GI surgery or prostatectomy. The use of anticoagulants may also give rise to hemorrhage. Certain natural proteins and vitamin K, as well as synthetic antagonists, are effective in controlling this bleeding. Blood transfusion is also an option for treating severe hemorrhage.

Vitamin K

Deficiency of vitamin K, a fat-soluble vitamin, is most common in older persons with abnormalities of fat absorption and in newborns, which are at risk of vitamin K deficiency bleeding. The deficiency is readily treated with oral or parenteral **phytonadione** (**vitamin K1**). Large doses of vitamin K1 are used to reverse the anticoagulant effect of excess warfarin. The response to vitamin k is slow, requiring about 24 hours to reduce INR (time to synthesize new coagulation factors). Thus, if immediate hemostasis is required, fresh frozen plasma should be infused.

Antiplasmin Agents

Antiplasmin agents are valuable for the prevention or management of acute bleeding episodes in patients with hemophilia and others with a high risk of bleeding disorders. Fibrinolytic states can be controlled by the administration of aminocaproic acid or tranexamic acid. Both agents are synthetic, orally active, excreted in the urine, and inhibit plasminogen activation. Tranexamic acid is 10 times more potent than aminocaproic acid. A potential side effect is intravascular thrombosis.

Protamine sulfate

Protamine sulfate *antagonizes* the anticoagulant effects of *heparin*. The positively charged *protamine* interacts with the negatively charged *heparin*, forming a stable complex without anticoagulant activity. Adverse effects of drug administration include hypersensitivity as well as dyspnea, flushing, bradycardia, and hypotension when rapidly injected.

Anemia:

Anemia is defined as a below-normal plasma hemoglobin concentration resulting from a decreased number of circulating red blood cells or an abnormally low total hemoglobin content per unit of blood volume. Anemia can be caused by chronic blood loss, bone marrow abnormalities, increased hemolysis, infections, drugs, malignancy, endocrine deficiencies, renal failure, and a number of other disease states.

AGENTS USED IN ANEMIAS:

IRON: Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as ferritin (an iron–protein complex) until needed by the body. Iron is delivered to the marrow for hemoglobin production by a transport protein, namely transferrin. Iron deficiency results from acute or chronic blood loss, from insufficient intake during periods of accelerated growth in children. Iron deficiency anemia is treated with oral or parenteral iron preparations. Oral iron corrects the anemia just as rapidly and completely as parenteral iron in most cases if iron absorption from the gastrointestinal tract is normal. An exception is the high requirement for iron of patients with advanced chronic kidney disease who are undergoing hemodialysis and treatment with erythropoietin; for these patients, parenteral iron administration is preferred. Oral preparations include ferrous sulfate, ferrous fumarate, ferrous gluconate, polysaccharide– iron complex, and carbonyl iron formulations. Of these preparations, ferrous sulfate is the most commonly used form of iron due to its high content of elemental iron and relatively low cost. Parenteral formulations of iron, such as *iron dextran*, *sodium ferric gluconate complex*, and *iron sucrose*, are also available. Gastrointestinal (GI) disturbances caused by local irritation (abdominal pain, constipation, diarrhea, etc.) and dark stools are the most common adverse effects of oral iron supplements. Parenteral iron formulations may be used in those who cannot tolerate oral iron. Fatal hypersensitivity and anaphylactic reactions can occur in patients receiving parenteral iron (mainly *iron dextran* formulations). Excessive iron can cause toxicities that can be reversed using chelators such as *Desferrioxamine iv or s/c infusion.*

Folic acid (folate): folic acid is required for normal DNA synthesis and its deficiency usually presents as megaloblastic anemia. The primary use of folic acid is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by
1) Increased demand (for example, pregnancy and lactation), 2) poor absorption caused by Pathology of the small intestine, 3) alcoholism, or 4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, methotrexate, pyrimethamine, and trimethoprim). Oral *folic acid* administration is nontoxic. There have been no substantiated side effects reported. Rare hypersensitivity reactions to parenteral injections have been reported.

Cyanocobalamin (vitamin B12):

Deficiencies of *vitamin B12* can result from either low dietary levels or, more commonly, poor absorption of the vitamin. Vitamin B12 deficiency can cause neurologic defects, which may become irreversible if not treated promptly. The vitamin may be administered orally (for dietary deficiencies), intramuscularly, or deep subcutaneously (for pernicious anemia). [Note: Folic acid administration alone reverses the hematologic abnormality and, thus, masks the vitamin B deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should not be treated with folic acid alone but, rather, with a combination of folate and vitamin B] Therapy must be continued for the remainder of the life of a patient suffering from pernicious anemia. This vitamin is nontoxic even in large doses. The 2 available forms of vitamin B12, cyanocobalamin and hydroxocobalamin, have similar pharmacokinetics, but hydroxocobalamin has a longer circulating half-life.

. **Erythropoietin and darbepoetin:**

Erythropoietin is produced by the kidney; reduction in its synthesis underlies the anemia of renal failure. EPO, thus, regulates red blood cell proliferation and differentiation in bone marrow. Human *erythropoietin* (*epoetin alfa*), produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, anemia associated with human immunodeficiency virus infection, and anemia in bone marrow disorders, anemias of prematurity, and anemias in some cancer patients.

Darbepoetin is a long-acting version of *erythropoietin* that differs from *erythropoietin* by the addition of two carbohydrate chains, which improves its biologic activity. *darbepoetin* has decreased clearance and has a half-life about three times that of *epoetin alfa.* Due to their delayed onset of action, these agents have no value in acute treatment of anemia.

The protein is usually administered intravenously in renal dialysis patients, but the subcutaneous route is preferred for other indications. Side effects may include elevation in blood pressure and arthralgia in some cases. [Note: The former may be due to increases in peripheral vascular resistance and/or blood viscosity.]

AGENTS USED TO TREAT SICKLE CELL DISEASE:

Hydroxyurea : Clinical trials have shown that *hydroxyurea* can reduce the frequency of painful sickle cell crises. *Hydroxyurea* is also used off-label to treat chronic myelogenous leukemia and polycythemia vera. Important side effects of *hydroxyurea* include bone marrow suppression and cutaneous vasculitis.

Pentoxifylline: Pentoxifylline is a methylxanthine derivative that has been called a “rheologic modifier.” It increases the deformability of red blood cells (improves erythrocyte flexibility) and reduces the viscosity of blood. This decreases total systemic vascular resistance, improves blood flow, and enhances tissue oxygenation in patients with peripheral vascular disease. It is indicated to treat intermittent claudication. It is available in extended-release tablets and is taken three times a day with food. Adverse reactions are mainly GI in nature and are lessened by administration with food.