BLEEDING DISORDERS

Hemostasis, the arrest of bleeding from an injured blood vessel. Hemostasis requires the combined activity of

- Vascular factors
- Platelets
- Plasma coagulation factors

hemostasis is localized to the area of tissue damage and is followed by removal of the clot and tissue repair. This is achieved by complex interactions between the vascular endothelium, platelets, coagulation factors, natural anticoagulants and fibrinolytic enzymes. Platelets and coagulation factors circulate in a non-activated state.

The stages of normal hemostasis:

platelets adhere; coagulation is activated. At the site of injury the endothelium is breaking,exposing subendothelial collagen.Tissue factor (TF) are released. Platelets bind to collagen via a specific receptor, glycoprotein Ia (GPIa), causing a change in platelet shape and its adhesion to the area of damage by the binding of other receptors (GPIb and GPIIb/IIIa) to von Willebrand factor and fibrinogen . Coagulation is activated by the tissue factor (extrinsic) pathway, generating thrombin. Platelet adhesion is mediated by von Willebrand's factor

The adherent platelets are activated by many pathways, including binding of Adenosine diphosphate (ADP), collagen, thrombin and adrenaline (epinephrine) to surface receptors. The cyclo-oxygenase pathway converts arachidonic acid from the platelet membrane into thromboxane A2, which causes aggregation of platelets. Activation of the platelets results in release of the platelet granule contents, enhancing coagulation.

Thrombin plays a key role in the control of coagulation: the small amount generated via the TF pathway massively amplifies its own production; the 'intrinsic' pathway becomes activated and large amounts of thrombin are generated. Thrombin enhances clot formation by cleaving fibrinogen to produce fibrin. Fibrin monomers are cross-linked by factor XIII, which is also activated by thrombin. Having had a key role in clot formation and stabilisation, thrombin then starts to regulate clot formation in two main ways: (a) activation of the protein C (PC) pathway (a natural anticoagulant), which reduces further coagulation; (b) activation of thrombin-activatable fibrinolysis inhibitor (TAFI), which inhibits fibrinolysis.

Once hemostasis has been established,, the propagation of clot is minimized by anticoagulants. **Antithrombin** is a serine protease inhibitor synthesised by the liver, which destroys activated factors such as XIa, Xa and thrombin (IIa). Its major activity against thrombin and Xa is enhanced by heparin and fondaparinux, explaining their anticoagulant effect.

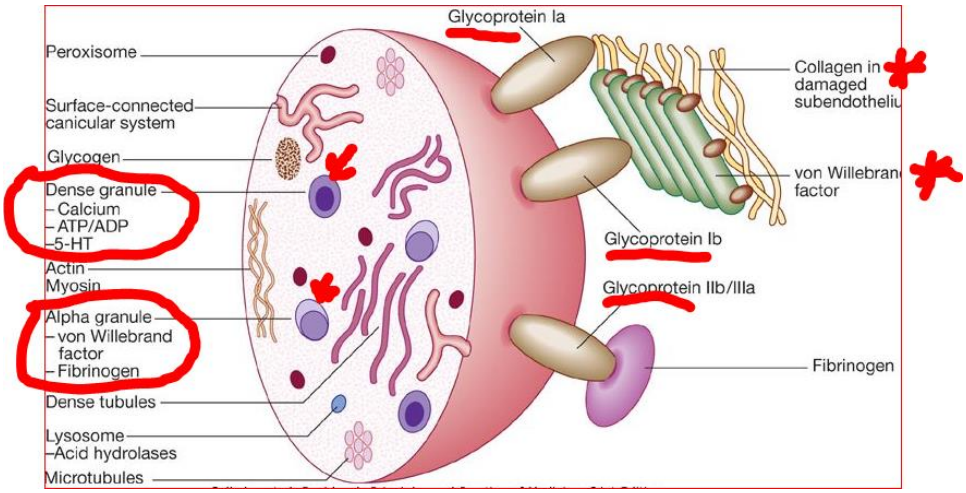
Tissue factor pathway inhibitor (TFPI) binds to and inactivates VIIa and Xa.

Activation of PC occurs following binding of thrombin to membrane-bound thrombomodulin; activated protein C (aPC) binds to its co-factor protein S (PS), and cleaves Va and VIIIa. PC and PS are vitamin K-dependent and are depleted by coumarin anticoagulants such as warfarin.

Plasmin *degrades fibrin to allow vessel recanalisation and tissue repair*. The insoluble clot needs to be broken down for vessel recanalisation. Plasmin, the main fibrinolytic enzyme, is produced when plasminogen is activated, e.g. by tissue plasminogen activator (t-PA) or urokinase in the clot. Plasmin hydrolyses the fibrin clot, producing fibrin degradation products including the D-dimer. This process is highly regulated; the plasminogen activators are controlled by an inhibitor called plasminogen activator inhibitor (PAI), the activity of plasmin is inhibited by α_2-antiplasmin and α_2-macroglobulin, and fibrinolysis is further inhibited by the thrombin-activated TAFI.

Hemostatic abnormalities can lead to bleeding or thrombosis. Bleeding can be due to congenital or acquired abnormalities in components of the hemostasis. The history and examination will help to clarify the severity and underlying cause of the bleeding problem.

Platelets are formed in the bone marrow from megakaryocytes. The formation and maturation of megakaryocytes are stimulated by thrombopoietin produced in the liver. Platelets circulate for 8-10 days before they are destroyed in the reticulo-endothelial system. Some 30% of peripheral platelets are normally pooled in the spleen and do not circulate. The surface membrane invaginates to form a tubular network, the canalicular system, which provides a canals for the discharge of the granules content(**α-granules, dense granules**) which secreting Von Willebrand factor ,fibrinogen,Calcium ,ADP , 5HT, epinephrine, serotonin leading to furthers activation, adhesion and aggregation of platelets.



Drugs which inhibit platelet function and thrombosis include aspirin (cyclo-oxygenase inhibitor), clopidogrel (inhibits adenosine diphosphate (ADP)-mediated activation), dipyridamole (inhibits phosphodiesterase), and the GpIIb/IIIa inhibitors abciximab, tirofiban and eptifibatide (prevent fibrinogen binding)

Clotting factors & Coagulation Cascade*-(look at the last page*)*

The coagulation system consists of a cascade of soluble inactive zymogen proteins designated by Roman numerals. When proteolytically cleaved and activated, each is capable of activating one or more components of the cascade. Activated factors are designated by the suffix 'a'. Some of these reactions require phospholipid and calcium. Coagulation occurs by two pathways; it is initiated by the extrinsic (or tissue factor) pathway and amplified by the intrinsic pathway

Clotting factors are synthesized by the liver, although factor V is also produced by platelets and endothelial cells. Factors II, VII, IX and X require post-translational carboxylation to allow them to participate in coagulation. The carboxylase enzyme responsible for this in the liver is vitamin K-dependent. Vitamin K is converted to an epoxide in this reaction and must be reduced to its active form by a reductase enzyme. This reductase is inhibited by warfarin, and this is the basis of the anticoagulant effect of warfarin

Congenital (e.g. hemophilia) and acquired (e.g. liver failure) causes of coagulation factor deficiency are associated with bleeding.

Bleeding history

- Site of bleed
- Duration of bleed
- Precipitating causes, including previous surgery or trauma
- Family history
- Drug history
- Other medical conditions, e.g. liver disease

Examination

There are two major patterns of bleeding:

1. Mucosal bleeding
It may be observed when reduced number or function of platelets (e.g. bone marrow failure or aspirin) or von Willebrand factor (e.g. von Willebrand disease)

- Skin: petechiae, bruises, post-surgical bleeding
- Gum and mucous membrane bleeding
- Fundal haemorrhage

2. Coagulation factor deficiency (e.g. haemophilia or warfarin)

- Bleeding into joints (haemarthrosis) or muscles
- Bleeding into soft tissues
- Intracranial haemorrhage
- Post-surgical bleeding

Investigation of coagulation

Bleeding disorders: In patients with clinical evidence of a bleeding disorder , there are recommended screening tests

Coagulation screening tests

Investigation	Normal range	Situations in which tests may be abnormal
Platelet count	150-400 × 10^9/L	Thrombocytopenia
Bleeding time----------	< 8 mins-----	Thrombocytopenia Abnormal platelet function von Willebrand disease Vascular and connective tissue abnormalities
Prothrombin time (PT)----------	9-12 secs	Deficiencies of factors II, V, VII or X Severe fibrinogen deficiency
Activated partial thromboplastin time (APTT)	26-36 secs	Deficiencies of factors II, V, VIII, IX, X, XI, XII Severe fibrinogen deficiency Unfractionated heparin therapy Antibodies against clotting factors Lupus anticoagulant
Fibrinogen concentration	1.5-4.0 g/L	Hypofibrinogenaemia, e.g. liver failure, disseminated intravascular coagulation

The extrinsic pathway is assessed by the prothrombin time (PT) and the intrinsic pathway by the activated partial thromboplastin time (APTT), sometimes known as the partial thromboplastin time with kaolin, (PTTK).
Clotting is delayed by deficiencies of coagulation factors and the presence of inhibitors of coagulation, e.g. heparin. If both the PT and APTT are prolonged, there is deficiency or inhibition of the final common pathway which includes factors X, V, prothrombin and fibrinogen, or global coagulation factor deficiency involving more than one factor. Further specific tests may be performed based on interpretation of the clinical scenario and results of these screening tests.
A mixing test with normal plasma allows differentiation between a coagulation factor deficiency (the prolonged time corrects) and the presence of an inhibitor of coagulation (the prolonged time does not correct); the latter may be chemical (heparins) or an antibody (most often a lupus anticoagulant but occasionally a specific inhibitor of one of the coagulation factors, typically factor VIII).
Von Willebrand disease may present with a normal APTT; further investigation of suspected cases is recommended (Ristocetin test)

Historically, bleeding time has been used to determine platelet function. it is non-specific so many centres have discontinued this test. Platelet function can be assessed in vitro by measuring aggregation in response to various agonists such as adrenaline (epinephrine), collagen, thrombin or ADP, or by measuring the constituents of the intracellular granules, e.g. ATP/ADP.

Coagulation screening tests are performed in patients with suspected disseminated intravascular coagulation (DIC) when clotting factors and platelets are consumed, resulting in thrombocytopenia and prolonged PT and APTT. In addition increased level of fibrin degradation products (D-dimers).

Monitoring anticoagulant therapy

The international normalised ratio (INR) is used to assess the therapeutic effect of coumarin anticoagulants, including warfarin. INR is the ratio of the patient's prothrombin time to that of a normal control, derived by comparison with an international reference standard material.

Monitoring of heparin therapy is only required with unfractionated heparins. Therapeutic anticoagulation prolongs the APTT relative to a control sample by a ratio of by 1.5-2.5. Low molecular weight heparins is not required monitoring by APTT.

Disorders of primary hemostasis

The initial formation of the platelet plug known as 'primary hemostasis' may be caused by thrombocytopenia ,von Willebrand disease , and also in platelet function disorders and diseases affecting the vessel wall.

Vessel wall abnormalities

Congenital causes such as :

1-Ehlers-Danlos disease

Vascular Ehlers-Danlos syndrome (type 4) is a rare autosomal dominant disorder (1 in 100 000) caused by a defect in type 3 collagen which results in fragile blood vessels and organ membranes, leading to bleeding and organ rupture. Classical joint hypermobility is often limited in this form of the disease but skin changes and facial appearance are typical. The diagnosis should be considered when there is a history of bleeding but normal laboratory tests.

2-Hereditary Hemorrhagic Telangiectasia:(Osler-Weber-Rendu)

Autosomal dominant genetic disorder that leads to abnormal blood vessel formation in the skin, mucous membranes, and often in organs such as the lungs, liver, and brain. May lead to epistaxis, acute and chronic G.I. bleeding with iron deficiency due to occult gastrointestinal bleeding. Treatment can be difficult because of the multiple bleeding points but regular iron therapy often allows the marrow to compensate for blood loss. Local cautery or laser therapy may prevent single lesions from bleeding. A variety of medical therapies have been tried but none has been found to be universally effective.

Acquired causes :

Scurvy:

Vitamin C deficiency affects the normal synthesis of collagen and results in general weakness, anemia, gum disease, and skin hemorrhages characterized by perifollicular and petechial haemorrhage, bruising and subperiosteal bleeding. The key to diagnosis is the dietary history Older adults who are not getting proper nutrition are most affected by scurvy.

Henoch-Schönlein purpura (HSP):

Acute immunoglobulin A (IgA)–mediated disorder characterized by a generalized vasculitis involving the small vessels of the skin, the gastrointestinal (GI) tract, the kidneys, the joints, and, rarely, the lungs and the central nervous system (CNS) .

symptoms develop as skin rash(95-100% of cases) as purpura , especially involving the legs.

Senile Purpura: dermal tissues atrophy and blood vessels become more fragile. due to an age-associated loss of subcutaneous fat and the collagenous support of small blood vessels. Drugs (e.g., corticosteroids, warfarin, aspirin, clopidogrel) may exacerbate the ecchymosis.

Others causes: excessive Corticosteroid Intake(skin bleeding, easy bruising) Infections like : Meningococcal meningitis Rocky Mountain spot fever also lead to skin bleeding

PLATELET DISORDERS:

Thrombocytopenia

Thrombocytopenia may be due to either increased platelet destruction , abnormal platelet distribution (an enlarged splenic pool), or decreased platelet production .

The symptoms and signs expected with various platelet counts are as follows:

Greater than 50,000/μL, no symptoms or signs, although patients may bleed longer with major trauma;
Between 25,000 to 50,000/μL, petechiae and bruising with minor trauma;
Between 10,000 to 25,000/μL, spontaneous petechiae and bruising greater on the lower extremities and menorrhagia;
less than 10,000/μL, prominent bruising, mucosal bleeding (epistaxis, gum bleeding, gastrointestinal [GI] or genitourinary [GU] bleeding), and a risk for central nervous system (CNS) bleeding.

Causes of Thrombocytopenia:

INCREASED PLATELET DESTRUCTION OR UTILIZATION
Immune destruction
Autoantibodies: ITP, disease-associated IT (collagen disease, lymphoproliferative disorders) Alloantibodies: post-transfusion purpura, neonatal purpura Drug-induced IT: quinidine, quinine, sulfonamides, gold, etc. Acute ITP Infection—HIV, hepatitis, cytomegalovirus, Epstein-Barr virus
Nonimmune destruction or platelet removal
Infection (bacterial, viral, malarial) Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome Disseminated intravascular coagulation Hemangiomas Platelet loss (massive bleeding)
Platelet redistribution (enlarged splenic pool)
Congestive splenomegaly Other (non-Hodgkin's lymphoma, Gaucher's disease, etc.)
DECREASED PLATELET PRODUCTION
Myeloproliferative disorders (acute or chronic leukemias, multiple myeloma, myelofibrosis) Lymphoproliferative disorders (non-Hodgkin's lymphoma, CLL) Bone marrow aplasia or hypoplasia (idiopathic, drug induced, radiation) Ineffective hematopoiesis (myelodysplasia, vitamin B_{12} or folate deficiency) Drugs (chemotherapy, thiazides, alcohol, etc.) Congenital/hereditary disorders

CLL =chronic lymphocytic leukemia; HIV =human immunodeficiency virus; IT =immune thrombocytopenia; ITP =immune thrombocytopenic purpura

Idiopathic Thrombocytopenic Purpura(ITP)

ITP can be divided into acute and chronic forms:

Acute ITP

More commonly seen in children, peak incidence at age 2 to 4 yr
Equal sex incidence
May follow a viral infection or vaccination
Usually runs a self-limiting course over 1-2 weeks , More than 80% of these children have a spontaneous remission

Chronic ITP

More common in young/middle-aged women
Tends to run a relapsing-remitting course

Evan's syndrome

ITP in association with autoimmune hemolytic anemia (AIHA)

The peak incidence of ITP in adults is at 20 to 40 yr of age, and the disease is much more common in women than in men (5:1). A number of patients will seek medical attention because of petechiae, purpura, epistaxis, or menorrhagia.

Except for clinical signs of bleeding (petechiae), the physical examination is usually unremarkable. enlarged spleen usually suggests a disorder other than ITP. In addition to the platelet count, a white blood cell count and hemoglobin level should be measured in adult patients.

ITP Dx:

ITP has normal white blood cells and hemoglobin, unless chronic bleeding would have caused an iron deficiency anemia. A bone marrow study may be useful to exclude other hematological disorders, especially if a splenectomy is planned. Other tests include those to detect the presence of antinuclear antibodies and rheumatoid factor, thyroid function tests, and serological tests for HIV.

Rx ITP in Adults:

Patients with moderate thrombocytopenia (platelets >30,000/ìL) with no history or signs of bleeding do not require therapy and should just be observed. In contrast, patients with clinical signs of bleeding or very low platelet counts, usually less than .20,000/L, require therapy.

Platelet transfusions may be required to control clinically significant bleeding but are not recommended for prophylaxis.

Steroids Initial therapy consists of corticosteroids (prednisone or prednisolone 1–2 mg/[kg · d]), which usually will raise the platelet count to safe levels in 70–80 % of the patients within 1 to 2 wk. When the platelet count has risen above 100,000/L, one can begin to taper the dose of corticosteroids down to 10–15 mg/d.

Only a few patients (10–20 %) will have long-lasting remissions following treatment with corticosteroids .

IV immunoglobulin (IVIG): has been the drug of second choice for many years.

Steroid Sparing Agent: Other medications like Immunosuppressive drugs as Rituximab ,Azathioprine, cyclophosphamide, cyclosporine, mycophenolate and tacrolimus are alternative treatment.

Splenectomy is indicated in patients who become unresponsive to corticosteroids or require high doses to maintain the platelet count at an acceptable level.

Prior to splenectomy

A vaccination with pneumococcal ,Hemophilus influenza and meningococcus vaccine should all be completed at least 2 weeks before a scheduled splenectomy to prevent a life-threatening infections.

Splenectomy will not only remove the major site of platelet destruction but also a source of platelet autoantibody production .After splenectomy 70 % of patients will sustain a long-term remission

New medications:

Romiplostim(Nplate): thrombopoietin receptor agonists(TPO-RA), given sub-cutaneously.

Eltrombopag is an orally available drug for treatment of chronic immune thrombocytopenic purpura (ITP) refractory to corticosteroids, immunoglobulins and/or splenectomy.

Thrombasthenia:

Functional disorders of platelets are relatively rare, and most of these disorders are mild. Thus, they may not be recognized early in life.

Inherited causes:

Bernard-Soulier syndrome: a rare autosomal recessive disease results from a deficiency of platelet glycoprotein protein (GPIb)

Glanzmann thrombasthenia: a rare autosomal recessive bleeding syndrome results from a deficiency of the GP IIb/IIIa complex. Platelets do not aggregate to any agents except ristocetin. The more severe type I results from a complete absence of the GP IIb/IIIa complex, whereas in the milder type II

Hermansky-Pudlak syndrome. is an extremely rare autosomal recessive disorder which results in oculocutaneous albinism (decreased pigmentation), bleeding problems due to a platelet abnormality (platelet storage pool defect).

Acquired causes :Antiplatelet drugs :

The most common acquired disorders of Platelet Function(thrombasthenia) are iatrogenic, resulting from the use of aspirin, clopidogrel, dipyridamole and the GP IIb/IIIa inhibitors to prevent arterial thrombosis.
Because aspirin irreversibly inactivates cyclooxygenase in platelets, its effect lasts throughout the life span of platelets, which is approximately 1 week.
Other NSAIDs are competitive inhibitors of cyclooxygenase, and their effect on platelets depends on the half-life of the drug. For example, the effect of ibuprofen, and most other NSAIDs, lasts only 1 day only.

Coagulation Cascade*