

Bleeding Disorders

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Haemostasis:

- Haemostasis refers to spontaneous arrest of bleeding caused by injury of small blood vessels.
- Small vessels are continuously exposed to trauma during normal activities can not bleed due to effects of haemostasis.

Functions of haemostasis:

- Maintains blood in a fluid, clot free state in normal vessel.
- Induce rapid and localized haemostatic plug at the site of injury.

Mechanism of haemostasis:

Haemostasis depends on three components

- Vascular wall
- Platelets
- Coagulation cascade

Events of haemostasis:

- After initial injury a brief period of arteriolar constriction due to reflex neurogenic mechanism, augmented by local secretion of vasoconstrictors such endothelin by endothelium.
- Endothelial injury exposes highly thrombogenic sub-endothelial matrix, which allow platelets to adhere through von-Willebrand factor to subendothelial tissue.
- Platelets become activated, that is it undergoes a shape change and release granule contents, particularly ADP and TX-A₂.
- Within minutes, released products recruit additional platelets to form a haemostatic plug. This is called primary haemostasis. The plug is called primary haemostatic plug.
- Tissue factors synthesized by endothelium is exposed at the site of injury. It acts in conjunction with secreted platelet factors to activate coagulation cascade and

for thrombin. Thrombin converts circulating soluble fibrinogen to insoluble fibrin threads.

- Fibrin threads bind to platelets firmly and converts primary platelet aggregates into a solid plug. This is called secondary haemostasis.
- Tissue plasminogen activator is simultaneously activated and prevents the extensive coagulation.

Haemorrhage and its Forms:

- **Haemorrhage** refers to extravasation of blood due to rupture of blood vessels. Haemorrhage may be external or may be enclosed within a tissue.
- **Haematoma** means accumulation of haemorrhagic blood in a tissue.
- **Petechiae** is minute 1 to 2 mm haemorrhage into skin, mucous membrane or serous surface.
- **Purpura** is haemorrhage larger than 3 mm into skin and mucous membrane.
- **Ecchymosed** is subcutaneous haematoma larger than 2 cm.
- Large accumulation of blood in body cavities like pleural cavity, peritoneal cavity, pericardial cavity, synovial cavity are called **haemothorax, haemoperitoneum, haemopericardium and haemarthrosis**, respectively.

Clinical Significance of Haemorrhage:

- Clinical effects of haemorrhage depend on volume and rate of blood loss.
- Rapid removal of up to 20% of blood volume or slow losses of even larger amount may have little impact in healthy adult. Greater losses may result in haemorrhagic shock.
- Site of haemorrhage is also important. Bleeding that would be trivial in subcutaneous tissue may cause death if located in the brain because the skull is unyielding and bleeding can result increased intracranial pressure and herniated.
- Chronic or recurrent external blood loss may lead to iron deficiency anaemia.

Haemorrhagic Disorders

Haemorrhagic disorders are a group of disorders of many different causes characterized by an abnormal tendency of bleeding due to failure of haemostasis.

Clinical Character of Haemorrhagic Disorders:

- Spontaneous bleeding in the skin, mucous membrane or internal tissue.
- Extensive or prolonged bleeding following trauma.
- Bleeding from more than one site.

Causes of Haemorrhagic Disorders:

- Due to vascular defects
- Due to platelet defects
- Due to coagulation defects.

- Combination of all

Bleeding due to vascular defects:

Common characters:

- More common but less severe
- Usually in the form of petechiae or purpura
- Increased bleeding time and frequently positive tourniquet test.
- Normal platelet count or function.
- Normal CT, APPTT, PT and TT

Classification of Vascular Bleeding Disorders:

Acquired:

- Simple easy bruising (devil's pinches)
- Senile purpura
- The symptomatic vascular purpura (non-thrombocytopenic purpura)
 - Infection
 - Drugs
 - Uraemia
 - Cushing's syndrome and adrenocorticosteroid administration
 - Scurvy
 - Dysproteinaemia
 - Henoch-Schoenlein purpura
- Miscellaneous
 - Orthostatic purpura
 - Mechanical purpura
 - Fat embolism
 - Auto-erythrocyte sensitization
 - Systemic disorders – collagen diseases, polyarteritis nodosa, amyloidosis, allergy

Congenital:

- Hereditary haemorrhagic telangiectasis (Osler-Rendu-weber disease)
- Ehlers-danlos disease

Senile Purpura:

- Usually occur in old age.
- A deficient supportive sub-endothelial connective tissue leads to easy rupture of vessels and bleeding occurs.
- Common sites of bleeding are extensor surface of forearm and hand.

Henoch-Schonlein Purpura:

- Also called allergic or anaphylactic purpura
- It is hypersensitivity disorder characterized by purpuric rash, colicky abdominal pain, polyarthralgia and acute glomerulonephritis.

- May follow certain foods or pollen, act as allergens, that evoke the formation of antibodies and antigen-antibody complex.
- Circulating immune complexes are deposited within vessels throughout the body and glomerular mesangial regions producing a generalized vasculitis.
- Vasculitis follows purpuric rash, abdominal pain due to focal gastrointestinal haemorrhage, polyarthralgia and AGN.

Hereditary Haemorrhagic Telangiectasis:

- An autosomal dominant disorder
- Dilated tortuous thin blood vessels bleed easily.

Ehler's Danlos Syndrome:

- Defect in collagen synthesis resulting in weak subendothelial connective tissue and produce bleeding.

Bleeding Due to Platelet Disorders

- Platelets are biconvex discs with a diameter of 2 to 4 μm .
- Platelet count normally ranges 1,50,000/cmm and 4,00,000/cm of blood.
- Platelet count below 1,50,000/cmm is called thrombocytopenia.
- Platelets play a significant role in arrest of bleeding by formation of haemostatic plug and activation of intrinsic pathway of coagulation.

Classification of Platelet Disorders:

- Thrombosthenia
- Thrombocytopenia

Thrombosthenia:

- Refers to the functional impairment of platelets leading to bleeding.
- Types:
 - Congenital
 - Membrane defects
 - Enzyme defects
 - Granule defects
 - Acquired
 - Stem cell disorders – leukaemia, myelodysplastic and myeloproliferative disorders etc.
 - Drugs – Indomethacin, midazole, acetylsalicylic acid etc.
 - Dys-proteinaemia – multiple myeloma and macroglobinaemia
 - Uraemia
 - Miscellaneous – antibodies, DIC, post-transfusion etc.

Defects in Platelet Number:

Thrombocytopenia:

- Thrombocytopenia refers to decreased number of platelet below the lower limit of normal range, 1,50,000/cmm of blood.
- It is the most common cause of abnormal bleeding.
- Bleeding is common when the count is less than 30,000 – 40,000/cmm of blood.
- Bleedings are associated with prolonged bleeding time.
- Clotting time, APTT, PT and TT are normal.

Aetiology of Thrombocytopenia:

Thrombocytopenia may results from

- Impaired platelet production
- Accelerated platelet destruction
- Dilution
- Splenic sequestration

Disorders Associated with Thrombocytopenia:

- **More common causes**
 - Idiopathic (immune) thrombocytopenic purpura (ITP)
 - Drugs and chemicals
 - Acute leukaemia
 - Aplastic anaemia
 - Bone marrow infiltration by – metastatic carcinoma, lymphoma. Multiple myeloma, myelofibrosis
 - Hyperplenism
 - DLE
- **Less common causes**
 - HIV infection
 - Megaloblastic anaemia
 - Liver diseases
 - Alcoholics
 - DIC
- **Rare causes**
 - Thrombotic thrombocytopenic purpura
 - Haemangioma
 - Food allergy

Idiopathic Thrombocytopenic Purpura (ITP)

- **Synonyms** – Immune thrombocytopenic purpura, auto-immune thrombocytopenic purpura, primary thrombocytopenic purpura, purpura haemorrhagica and Werlhof's disease.
- It is a haemorrhagic disorder characterized by thrombocytopenia in almost all cases due to antibody formation.

Pathogenesis:

- ITP is virtually always due to antiplatelet antibodies.
- IgG antibodies may be identified in majority of cases.
- Thrombocytopenia is due to antibody-mediated platelet destruction.

Clinical features:

- May occur in any age but is most common in children and young adults.
- Until the age of about 12 years, the sex incidence is apparently equal, but thereafter females are affected 3-4 times more commonly than males.
- Types – acute and chronic.

Types and Sites of Bleeding:

- Bleeding occurs spontaneously.
- Also occurs following trauma, surgery and dental procedure.
- Bleeding from wound tends to occur at once, ceases within 48 hours, and does not recur.
- Skin is the most common site of haemorrhage.
- Haemorrhage may be in the form of multiple petechiae or ecchymoses, or both.
- Bleeding from mucous membrane is common.
- Epistaxis, gum bleeding, menorrhagia, metrorrhagia, melena are not infrequent.
- Haematemesis and haemoptysis is less common.
- Bleeding in internal organs is relatively uncommon, but may be serious.
- Anaemia may be present or absent according to severity of bleeding.
- Subconjunctival haemorrhage, enlarged spleen may be present.
- No lymph node enlargement, no sternal tenderness.

Blood Picture:

- Thrombocytopenia in all degrees, values ranging from just below normal to less than 10,000/cmm.
- Sometimes, platelets appear to be morphologically abnormal with large and atypical forms.
- Bleeding time (BT): prolonged
- Tourniquet test: Positive
- Clotting time (CT): Normal
- Prothrombin time (PT): Normal
- Activated partial thromboplastin time (APTT): Normal
- Thromboplastin time (TT): Normal
- Haemoglobin level: is proportional to the degree of blood loss. Red cells are microcytic and hypochromic due to iron loss.
- ESR: usually normal
- Anticardiolipin antibody: positive in 30%.

Bone Marrow:

- Megakaryocytes and their precursors are present in normal and often in increased in number.
- Percentage of immature megakaryocytes are increased. Features of immature megakaryocytes are
 - It is usually small and round
 - Nucleus is unilobular, round and smaller than mature megakaryocytes. Nuclei contains relatively loose hyperchromatic chromatin.
 - Cytoplasm is small in amount, more bluish, and usually contains vacuoles, and few platelet granules or agranular.
- In a few cases, there is moderate increase in mature lymphocytes, or in eosinophils.
- In case of severe haemorrhage, there may be erythroid hyperplasia.

Salient Features of ITP:

- Is an auto-immune disorder.
- Blood film shows thrombocytopenia in variable degrees with fragmented and large forms.
- Antibodies IgG is produced against platelet specific antigen.
- Thrombocytopenia is due antibody-mediated platelet destruction.
- Bone marrow usually shows increased megakaryocytes with immature forms.
- More common in children below 10 years.
- Main site of platelet destruction is spleen.
- Splenectomy produces remission in most of the patients with chronic ITP.

Coagulation Disorders

Physiology:

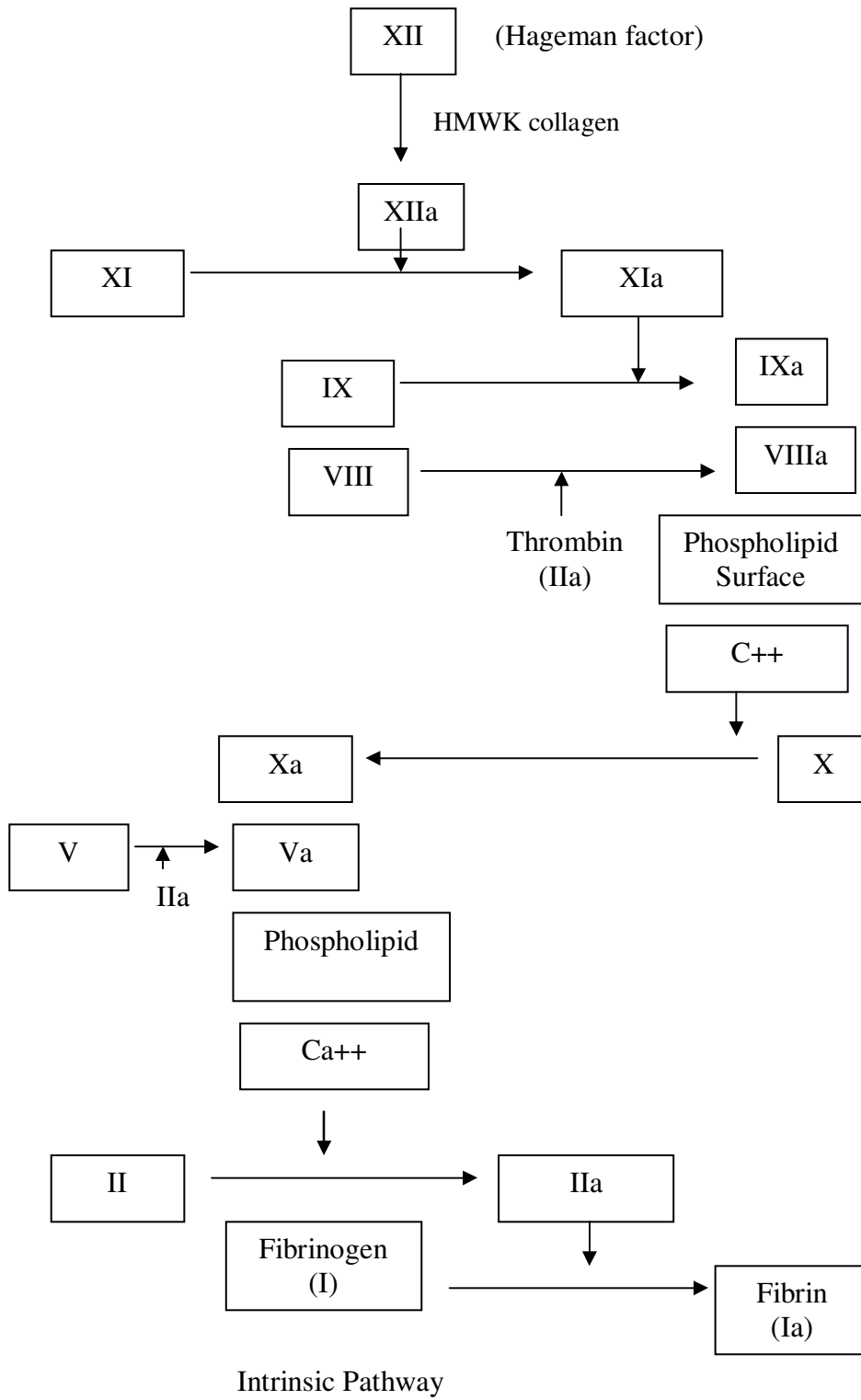
- Coagulation system constitutes the third important component of the haemostatic process.
- Traditionally blood coagulation pathways are divided into extrinsic and intrinsic pathway.
- Coagulation factors of intrinsic pathways are XII, XI, IX and VIII.
- Tissue factor (thromboplastin) and VII constitute the extrinsic pathways.

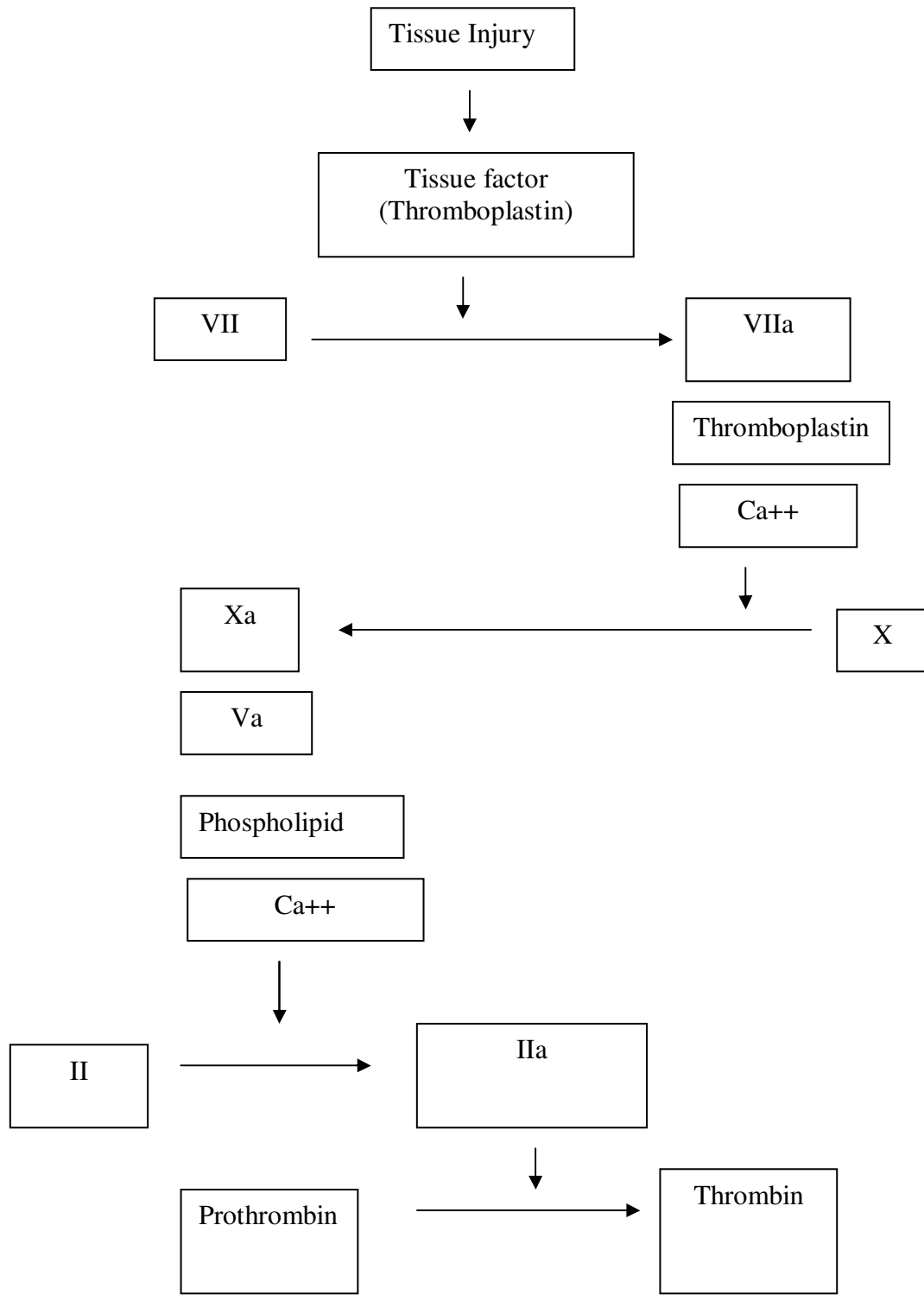
Intrinsic Pathway:

- In intrinsic pathway, factor XII is activated by kallikrein and also ultimately by auto-activation by factor XIIa itself.
- Factor XIIa activate XI and forms active XIa which interacts with factor IX and produce active IXa. (Factor IX is also activated by factor VIIa of extrinsic pathway).
- Factor IXa forms a complex with XIIIa, Ca^{++} , and phospholipids to complete the factor X activator, termed tenase. A similar complex is assembled by factor Xa, factor Va, Ca^{++} and phospholipids to form the prothrombin activator called prothrombinase. (Prothrombinase is also produced by extrinsic pathway)

Extrinsic Pathway:

- Factor XII is activated by tissue factor.
- Activated factor VIIa can activate factor X and helps in the formation of prothrombinase.
- Prothrombinase interacts with prothrombin to form thrombin, which convert soluble fibrininogen into fibrin threads.
- Factor XIIIa acts on fibrin threads and cross-link fibrin threads, then stabilize the clot.





Extrinsic Pathway

Anticoagulation System:

- Anticoagulation system prevent extensive coagulation and thereby localize the clot at the site of vascular injury.
- Inhibitors of coagulation and their target coagulation factors

Inhibitors	Target
Antithrombin III	Xa, thrombin
Heparin co-factor II	Thrombin
α_2 -macroglobulin	Thrombin, kallikrein
Protein C	Factor Va, VIIa
Protein S	Co-factor for activated Protein C

Bleeding Due to Coagulation defects:

- Bleeding results from either qualitative or quantitative deficiency of coagulation factors.
- Bleeding occurs usually in deep tissue.
- Commonly manifests as large echymoses or haematoma after a trauma or as prolonged bleeding after any surgical procedure.
- Haemarthrosis is the characteristic manifestation of coagulation disorder.

Classification of Coagulation Disorders:

- Acquired – Usually multiple factors are involved
- Hereditary – Usually single factor is involved

Acquired Coagulation Disorders:

The followings disorders are associated with acquired coagulation disorders:

1. Vitamin K deficiency
 - a. Obstructive jaundice
 - b. Coeliac disease
 - c. Liver disease
 - i. Defective synthesis of coagulation factors (I, II, V, VII, IV and X)
 - ii. Increased fibrinolytic activity
 - iii. Intravascular coagulation
2. Anticoagulant drugs
3. Disseminated intravascular coagulation
4. Active fibrinolysis
5. Massive transfusion of stored blood
6. Circulating inhibitors of coagulation

Hereditary Coagulation Disorders:

- Usually single coagulation factor is involved.
- Any coagulation factor may be affected.
- Factor VIII and IX are commonly involved.

Common Hereditary Coagulation Disorders:

1. Haemophilias
 - a. Haemophilia A – Factor VIII deficiency
 - b. Haemophilia B – factor IX deficiency
2. von-Willebrand disease
3. Other congenital deficiency disorders
 - a. Fibrinogen deficiency
 - b. Factor V deficiency
 - c. Factor XIII deficiency

Physiology of Factor VIII and vWF Complex:

- It contains factor VIII and vWF; 99% of its weight is due to vWF.
- These two factors are synthesized by separate genes and combined with each other in blood to form factor VIII-vWF complex.
- vWF are synthesized from endothelium and platelets.
- Factor VIII is synthesized from liver and endothelium.

Functions of factor VIII:

- Helps in the formation of prothrombin activator, which form thrombin from prothrombin.
- Thrombin converts soluble fibrinogen into insoluble fibrin.

Functions of vWF:

- It bridges between plates by binding the receptor mainly glycoprotein Ib-Ix complex on platelets and subendothelial collagen tissue.
- It acts as a carrier of factor VIII and protects them from rapid catabolism.
- The half life of factor VIII is 12 hours, when circulating vWF is normal. But half life of factor VIII is decreased of 2.4 hours if vWF is deficient in quality and quantity.

Von Willebrand Disease

Important Features:

- It is an autosomal dominant disease.
- It affects both sexes.
- It is manifested with bleeding on skin mucous membrane. Bleeding time is prolonged due to defective platelet adhesion to subendothelial tissues. Patients also present with deep-seated haemorrhages caused by factor VIII deficiency.

Variants of von Willebrand Disease on the basis of Pathophysiology:

Variants	Features
Type 1 Classical	<ul style="list-style-type: none"> a. Factor VIII activity (VIII : C); low b. von Willebrand factor antigen (vWF : Ag); low c. Ristocetin co-factor (vWF : Rc); low
Type 1Ia	<ul style="list-style-type: none"> a. Factor VIII activity (VIII : C); normal or low b. von Willebrand factor antigen (vWF : Ag); normal or low (abnormal electrophoresis) c. Ristocetin co-factor (vWF : Rc); very low (Prolonged bleeding time)
Type 1Ib	<ul style="list-style-type: none"> a. Factor VIII activity (VIII : C); normal or low b. von Willebrand factor antigen (vWF : Ag); normal or low (abnormal electrophoresis) c. Ristocetin co-factor (vWF : Rc); Normal or low
Type 1II (Severe)	<ul style="list-style-type: none"> a. Factor VIII activity (VIII : C); low b. von Willebrand factor antigen (vWF : Ag); low c. Ristocetin co-factor (vWF : Rc); low d. All activities are very low or absent (recessive transmission)

Laboratory Findings:

- Bleeding time: prolonged
- Clotting time: Prolonged
- APTT: Prolong and corrected by plasma but not by serum.
- Prothrombin time: Normal
- Thrombin time: Normal
- Platelet count: Normal
- Factor VIII assay: Reduced.
- Tourniquet test: May be positive.

Haemophilia

- It is severe and often fatal haemorrhagic disorder that affects usually the male children.
- Haemophilia is the classic example of X-linked recessive disorder.
- The defective gene is located on X chromosome.
- In the male who lacks a normal allele, the defect is manifested by clinical haemophilia.
- The affected male will not transmit the disorder to his son, because his Y chromosome can not carry the haemophilic gene. However, all the daughters will be carrier of haemophilia because they inherit his X chromosome containing haemophilic gene.
- Most of these women will unaffected clinically because of presence of a normal allele from mother.
- The female carrier will transmit the disorder to half of her sons and carrier state to half of her daughters.

Important Characters:

- It is an X-linked recessive disorder.
- Heterozygous male and homozygous female are usually affected.
- Sometimes female in heterozygous state with unfavourable lyonization may be affected.
- Female in Turner's syndrome (XO), can also be affected when normal X is absent.
- 70% haemophilic patients have family history. Rest 30% result from new mutation.

Classification of Haemophilia:

On the basis of affected factor

- Haemophilia A (True haemophilia or Classic haemophilia) – Characterized by factor VII deficiency.
- Haemophilia B (Christmas disease) – Characterized by factor IX deficiency.

On the basis of clinical presentation

- Mild – 5 to 30% of factor activity and mild bleeding may occur with major trauma or surgery.
- Moderate – 1 to 5% of factor VIII activity and moderate bleeding with minimal trauma or surgery.
- Severe – 0 to 1% of factor VIII activity and severe spontaneous bleeding such as haemarthrosis.

Clinical features:

- Age: Infant and children are affected.
- Sex: male is usually sufferer.
- Bleeding manifestations.
 - Haemarthrosis – painful, tender, warm and swollen joint.
 - Large ecchymoses, subcutaneous and intramuscular haematomas are usually present.
 - Haemorrhage from mouth, gums, lips, frenulum and tongue are frequently found.
 - Haematemesis and melena not uncommon.
 - Haematuria can also occur.
 - Wound bleeding is slow, and persists for days and weeks. Delayed bleeding is common from wound.
 - Skin bleeding, a tendency to bruise excessively after a minor injury is frequently present.
 - Intracranial haemorrhage is not uncommon.

Complications of Bleeding:

- Pain
- Anaemia
- Constitutional disturbances like fever.
- Chronic haemophilic arthritis.
- Pressure effects of haematomas on vital structures.

Laboratory Findings:

- a. Bleeding time: Normal.
- b. Clotting time: Prolonged.
- c. APTT: prolonged and corrected by fresh plasma but not serum.
- d. Prothrombin time: Normal
- e. Thrombin time: Normal
- f. Platelet count: Normal.
- g. Confirmatory test:
 - Factor VIII and IX assay:
In haemophilia A, factor VIII is decreased.
In haemophilia B, factor IX is decreased.

Investigation of a Patient with Bleeding Tendency

Three questions must be answered:

1. Is the bleeding due to local pathological lesion, a haemorrhagic disorder, or a combination of two ?
 2. If due to haemorrhagic disorder, which of the components of the haemostatic mechanism is affected ?
 3. What is cause of haemorrhagic disorder ?
- Diagnosis of many haemorrhagic disorders is largely or wholly clinical.
 - Selection of appropriate laboratory tests required for appropriate diagnosis depends on the full clinical assessment.

Clinical Features that Should be Sought

History

- Age, sex
- Present episode of bleeding
 - Type of bleeding: petechiae, echymoses, haematoma, deep tissue or joint bleeding, wound haemorrhage, menorrhagia, mucous membrane bleeding
 - frequency and duration
 - Apparent cause: spontaneous or following trauma or surgery.
- Co-existing disease
 - Disorders that may cause vascular bleeding
 - Disorders that may cause thrombocytopenia
 - Disorders that may cause coagulation defect
 - Gastrointestinal disease
 - Renal disease
 - Liver disease
 - Splenomegaly
 - primary haemopoietic disorders
 - other possible association, e.g. pregnancy, allergic reaction, skin disorders
- Drug ingestion
 - Aspirin, NSAID
- Anticoagulant administration
 - Warfarin
 - Phenindione
- Occupation
 - Exposure to drugs and chemicals
 - Hazards of trauma
- Diet
 - Ascorbic acid intake
- Past history bleeding and trauma

- Age at occurrence of first abnormal bleeding and details of incidence
- Haemorrhagic incidents
 - Ecchymoses – traumatic and/or spontaneous
 - Haematomas – cause, size duration
 - Petechial haemorrhages
 - Epistaxis – cause, severity, frequency
 - Minor wound bleeding
 - Haematemesis, Melaenena, haemoptysis, haematuria – cause and severity
 - Menstrual bleeding and post-partum bleeding – severity, duration
- Bleeding after trauma and surgery
 - Tooth extraction, tonsilectomy, circumcision, major surgery, accidents – time, duration, severity and recurrence
- Therapeutic measure and response
 - Blood transfusion, wound suturing, cautery, pressure bandages, splenectomy, corticosteroids, vitamin K
- Family history of bleeding
 - Bleeding episodes in siblings and children
 - History in antecedents, both paternal and maternal

Physical Examination

- General appearance
 - Cushingoid, myxoedematous, plethoric, icteric, cachectic
- Skin
 - Telangiectases, haemangiomas, petechiae, urticaria, ecchymoses, texture and elasticity of skin, scars.
- Mouth
 - Petechiae, telangiectases, lacerations, haematoma
- Wounds
 - Excessive blood clot, degree of healing, nature of scars
- Abdomen
 - Superficial venous engorgement, haematoma in abdominal wall, hepatomegaly, splenomegaly, abdominal masses, ascites
- Pelvis
 - Rectal and vaginal examination (if indicated)
- Nervous system
 - Fundus oculi – retinal haemorrhage, papilloedema
 - Peripheral nerve – sensory and motor
- Joints
 - Swelling, tenderness and deformity
- Urine
 - Proteinuria, haematuria, haemoglobinuria
- Tourniquet test

Special Investigations

- Essential investigations for all cases
 - Full blood examination
 - Haemoglobin
 - Red cell morphology
 - White cell count
 - Platelet count and examination of a blood film for number, morphology, and presence of platelet clumping
 - Skin bleeding time
- Further investigations that may require
 - Prothrombin time
 - Activated partial thromboplastin time
 - Factor assay
 - Test of platelet aggregation

Is the bleeding due to local pathological lesion, a haemorrhagic disorder, or a combination of two ?

- For consideration of types of bleeding
- Consideration about past bleeding and existence of predisposing factor
- Haemorrhagic disorder is suspected
 - Spontaneous bleeding
 - Excessive or prolonged bleeding after minor trauma
 - Bleeding from more than one site

If due to haemorrhagic disorder, which of the components of the haemostatic mechanism is affected ?

Platelet disorder

- Petechial bleeding common
- Ecchymoses numerous
- Mucous membrane bleeding is prominent
- Tourniquet test positive
- Bleeding time prolonged
- Platelet count reduced

Vascular disorder

- Bleeding usually confined to skin
- Petechiae or ecchymoses
- Platelet count normal
- Clotting tests normal

Coagulation disorder

- Petechial bleeding is rare
- Larger ecchymoses
- More frequently in deep tissue
- One or more of clotting tests is abnormal

What is cause of haemorrhagic disorder ?

- The cause is determined from a consideration of the history and examination and certain special tests.
- A long history of abnormal bleeding is the strong evidence of congenital haemorrhagic disorder.

Haemostatic Blood Products

These are derivative of blood commonly used in the treatment of patients of coagulation defects. Commonly used products are

- Fresh whole blood
- Platelet concentrates
- Fresh frozen plasma
- Factor VIII concentrates
- PPSB (factors II, VII, IX X)
- Prothrombinex (factor II, IX)
- Fibrinogen

- O -