بسم الله الرحمن الرحيم

Hemostasis

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Hemostasis

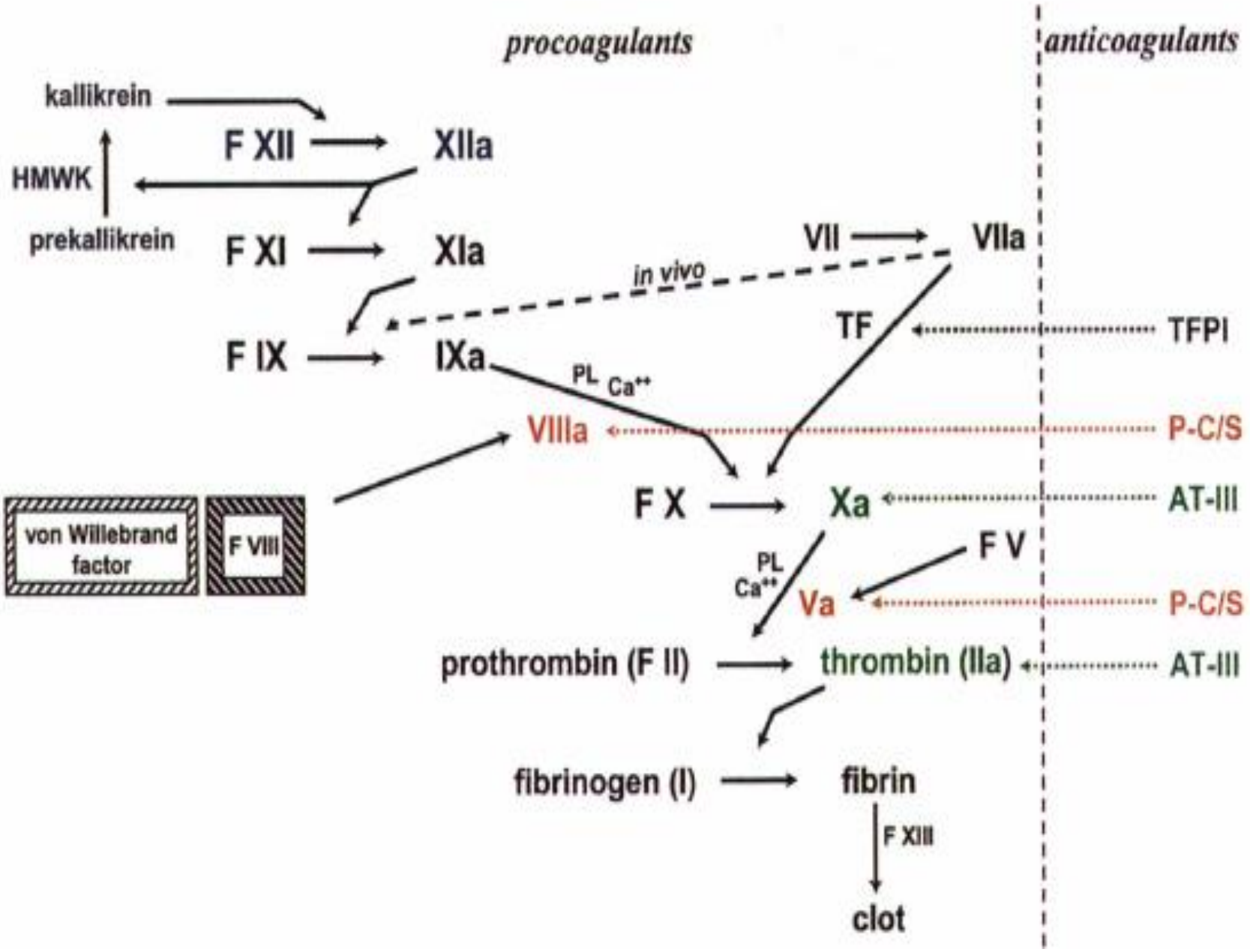
- After vascular injury, vasoconstriction occurs and flowing blood comes in contact with the subendothelial matrix.
- von Wille brand factor (VWF) changes conformation and provides the glue to which the platelet VWF receptor binds

Hemostasis

- After adherence, platelets become activated and release storage granules containing adenosine diphosphate (ADP), thromboxane A2,and other stored proteins. These trigger the aggregation and recruitment of other platelets to form the platelet plug

Hemostasis

- One of the subendothelial matrix proteins that is exposed after vascular injury is tissue factor, binds to factor VII, and activates the clotting cascade.


procoagulants
anticoagulants
kallikrein
F XII
XIIa
HMWK
prekallikrein
F XI
XIa
VII
VIIa
in vivo
TF
TFPI
F IX
IXa
PL Ca++
VIIIa
P-C/S
von Willebrand factor
F VIII
F X
Xa
AT-III
F V
PL Ca++
Va
P-C/S
prothrombin (F II)
thrombin (IIa)
AT-III
fibrinogen (I)
fibrin
F XIII
clot

Hemostasis

- Thrombin clots fibrinogen into fibrin, activates factors V, VIII, and XI, and aggregates
- platelets. Thrombin also activates factor XIII. The stable fibrin-platelet plug is ultimately formed through clot retraction and cross linking of the fibrin clot by factor XIIIa.

Hemostasis

- Thrombin binds to thrombomodulin, its endothelial receptor. The thrombin-
- thrombomodulin complex then activates protein C into activated protein C

- . In the presence of the cofactor protein S,
- activated protein C proteolyses and inactivates factor Va and factor VIIIa.

- AT-III is a serine protease inhibitor that regulates factor Xa and thrombin primarily and also, to a lesser extent, factors IXa, Xla, and XIIa.

Hemostasis

- The final inhibitor is TFPI, which quickly shuts down the activation of factor X by factor VII and tissue factor and shifts the activation site of tissue factor and factor VII to that of factor IX

Hemostasis

- Once a stable fibrin-platelet plug is formed, the fibrinolytic system limits its extension and also lyses the clot (fibrinolysis) to re-establish vascular integrity.

- Plasmin, generated from plasminogen
- degrades the fibrin clot. In the process of dissolving the fibrin clot, fibrin degradation products are produced.

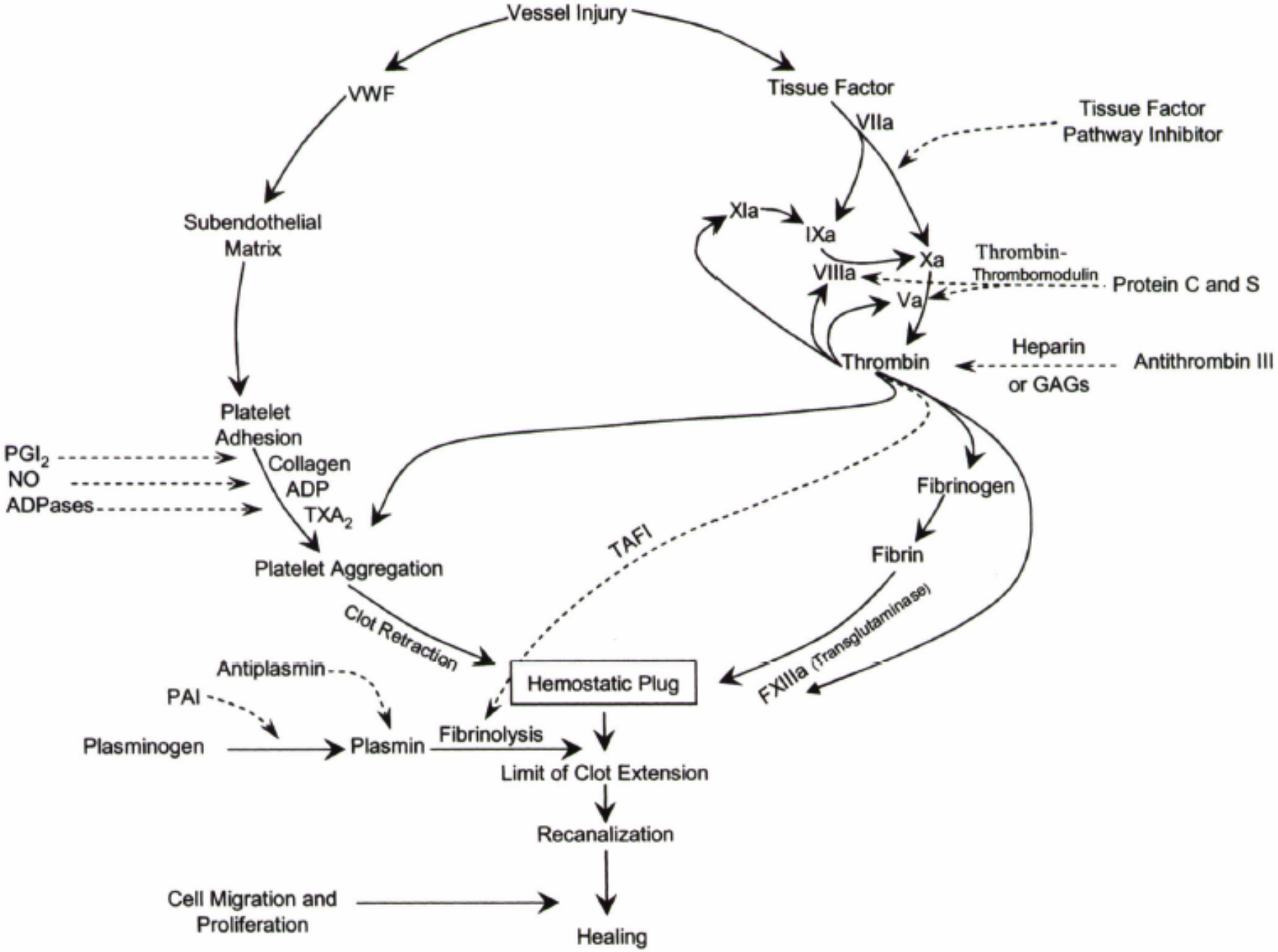


Figure 475-2. The hemostatic mechanism. ADP, adenosine diphosphate; GAGs, glycosaminoglycans; NO, nitric oxide; PGI_2, prostacyclin; PAI, plasminogen activator inhibitor; TAFI, thrombin-activated fibrinolytic inhibitor; TXA_2, thromboxane A_2; VWF, von Willebrand factor.

CLINICAL AND LABORATORY EVALUATION OF HEMOSTASIS

HISTORY

- For most hemostatic disorders, the clinical history provides the most useful information.

HISTORY

- The site or sites of bleeding, the severity and duration of hemorrhage, and the age at onset. Was the bleeding spontaneous, or did it occur after trauma? Was there a previous personal or family history of similar problems? Did the symptoms correlate with the degree of injury or trauma? Does bruising occur spontaneously? If the patient had previous surgery or significant dental procedures, was there any increased bleeding? If a child or adolescent has had surgery affecting the mucosal surfaces, such as a tonsillectomy or major dental extractions, the absence of bleeding usually rules out a hereditary bleeding disorder.

- In postpubertal females, it is important to take a careful menstrual history. Women with mild VWD who have a moderate history of bruising frequently have a reduction of that bruising during pregnancy or after administration of oral contraceptives. Some medications, such as aspirin and other nonsteroidal anti-inflammatory drugs, may inhibit platelet function and increase bleeding symptoms in patients with a low platelet count or abnormal hemostasis.

PHYSICAL EXAMINATION

- Mucous membranes or skin (mucocutaneous bleeding)
- Muscles and joints (deep bleeding).

PHYSICAL EXAMINATION

- Patients with defects in platelet-blood vessel wall interaction (VWD or platelet function defects) usually have mucocutaneous bleeding, which may include epistaxis, menorrhagia, petechiae, ecchymoses, occasional hematomas, and less commonly, hematuria and gastrointestinal bleeding.

PHYSICAL EXAMINATION

- Individuals with a clotting factor deficiency,
- such as hemophilia (factor VIII or factor IX deficiency), have symptoms of deep bleeding into muscles and joints, with much more extensive ecchymoses and hematoma formation.

LABORATORY TEST

- platelet count,PT, and partial thromboplastin time (PIT). If the results are normal, a thrombin time to evaluate fibrinogen function and VWF testing should be considered.

LABORATORY TEST

- In a patient with an abnormal bleeding history and a positive family history, normal screening tests should not preclude further laboratory evaluation.

Bleeding Time

- Bleeding time assesses the function of platelets and their interaction with the vascular wall.
- 4-8 min

Platelet Function Analyzer

- The PFA-lOO measures platelet
- adhesion-aggregation in whole blood at high shear when exposed to either collagen-epinephrine or collagen-ADP.

Platelet Count

- Thrombocytopenia is the most common acquired cause of a bleeding diathesis in children.
- platelet count of >50,000/mm3 rarely have
- significant clinical bleeding.

PROTHROMBIN TIME AND ACTIVATED PARTIAL THROMBOPLASTIN TIME.

- Intrinsic (surface activation)
- Extrinsic (tissue factor-mediated) pathways.

- PT measures the activation of clotting by tissue factor (thromboplastin) in the presence of calcium.
- PT is not prolonged with deficiencies of factors VIII, IX, XI,or XII.

- normal PT is 10-13 sec. PT has been standardized using the International Normalized Ratio (INR).
-

Partial Thromboplastin Time

- It does not measure factor VII, factor XIII.

Thrombin Time.

- Thrombin time measures the final step in the
- clotting cascade, in which fibrinogen is converted to fibrin.
- 11-15 sec

- Prolongation of thrombin time occurs with reduced fibrinogen levels *(hypofibrinogenemia or afibrinogenemia), with* dysfunctional fibrinogen *(dysfibrinogenemia), or with the use of* substances that interfere with fibrin polymerization, such as heparin or fibrin split products.

Reptilase Time.

- Unlike thrombin time, reptilase time is not sensitive to heparin and is prolonged only by reduced or dysfunctional fibrinogen and fibrin split products.

Mixing Studies

- Normal plasma is added to the patient's plasma, and PT or PTT is repeated.
- Correction of PT or PTT by 1:1 mixing with normal plasma suggests deficiency of a clotting factor, because a 50% level of individual clotting proteins is sufficient to produce normal PT or PTT.

- An inhibitor of clotting is a chemical similar to heparin that delays coagulation or an antibody directed against a specific clotting factor or the phospholipid used in clotting tests. In the inpatient setting, the most common cause of this finding is heparin contamination of the sample.

- If the mixing study is not corrected or if it becomes more prolonged and the patient has clinical bleeding, an inhibitor of a specific
- clotting factor (antibody directed against the factor), most commonly factor VIII, factor IX, or factor XI, may be present.

- If the patient has no bleeding symptoms and both PTT and the mixing study are prolonged, a lupus-like anticoagulant is often present.
- These patients usually have a long PTT, do not
- bleed, and may have a clinical predisposition to excessive clotting

Clotting Factor Assays

- 100% activity is expressed as 100 IU/dL.
- By definition, 1 international unit (IU) of each factor is defined as that amount in 1 mL of normal plasma.
- In general, severe deficiency of factor VIII or factor IX is <1 IU/dL (<1% of normal), moderate deficiency is 1-5 IU/dL, and
- mild deficiency is >5 IU/dL,

- One Bethesda unit is defined as the amount that will inhibit 50% of the clotting factor in normal plasma.

Platelet Aggregation

- Platelet-rich plasma from the patient is activated with 1 of a series of agonists (ADP, epinephrine, collagen, thrombin or thrombinreceptor peptide, and ristocetin).

Testing for Thrombotic Predisposition

- (protein C, protein S, AT-III)

Testing for Thrombotic Predisposition.

- Factor V Leiden is a common mutation in factor V that is associated with a significant risk of thrombosis. A point mutation in the factor V molecule prevents the inactivation of factor Va by
- activated protein C and, thereby, the persistence of factor Va. This defect is also known as *activated protein C resistance and is easily*
- diagnosed by DNA testing.

- The prothrombin gene mutation (G20210A) is a mutation in
- the noncoding portion of the prothrombin gene. This mutation increases the amount of prothrombin messenger RNA is associated with elevated levels of prothrombin.

- Elevated Homocysteine. Levels of homocysteine may be increased as a result of genetic mutations, causing homocystinuria.
- Such patients are predisposed to arterial and venous thrombosis as well as to an increase in arteriosclerosis.

DEVELOPMENTAL HEMOSTASIS

- The normal newborn infant has a reduced level of most procoagulants and anticoagulants.

- The extremely premature infant will have
- prolonged PT and PTT as well as a marked reduction in anticoagulant
- proteins (protein C, protein S, and AT-III).

- Levels of fibrinogen,factors V and VIII, VWF, and platelets are near-normal

FACTOR VIII OR FACTOR IX DEFICIENCY (HEMOPHILIA A OR B)

- Deficiencies of factors Vlll and IX are the most common severe inherited bleeding disorders.
- Inadequate thrombin generation leads to failure to form a tightly cross-linked fibrin clot to support the platelet plug. Patients with hemophilia slowly form a soft, friable clot.

- Neither factor Vlll nor factor IX crosses the placenta; bleeding symptoms may be present from birth or may occur in the fetus.
- 30% of male infants with hemophilia bleed with circumcision.
- Thus, in the absence of a positive family history (hemophilia has a high rate of spontaneous mutation), hemophilia may go undiagnosed in the newborn.

- Even in patients with severe hemophilia, only 90% have evidence of increased bleeding by 1 yr of age.
- hallmark of hemophilia is hemarthrosis.
- Ankle, knees and elbows
- "target" joint
- iliopsoas muscle

- If head trauma is of sufficient concern to suggest radiologic evaluation, factor replacement should precede radiologic evaluation.
- Life-threatening hemorrhages require replacement therapy to achieve a level equal to that of normal plasma (100 IU/dL, or 100%).

- Patients with mild hemophilia who have factor Vlll or factor IX levels of >5 IU/dL usually do not have spontaneous hemorrhages.

LABORATORY FINDINGS AND DIAGNOSIS.

- PTT
- Assay for factors VIII and IX will confirm the diagnosis of hemophilia.

DIFFERENTIAL DIAGNOSIS

- severe thrombocytopenia;
- severe platelet function disorders, such as Bernard-Soulier syndrome and
- Glanzmann thrombasthenia;
- type 3(severe) von Willebrand disease; and vitamin K deficiency.

GENETICS AND CLASSIFICATION

- 1:5,000 males
- with 85% having factor VIII deficiency
- and 10-15% having factor IX deficiency.

- Severe hemophilia is characterized by having <1% activity of the specific clotting factor, and bleeding is often spontaneous.
- Patients with moderate hemophilia have levels of 1-5% and require mild trauma to induce bleeding.
- Mild hemophilia have levels of >5%, frequently require significant trauma
- to cause bleeding.

- The hemostatic level for factor VIII is
- >30-40%, and for factor IX, it is >25-30%. The lower limit of levels for factors VIII and IX in normal individuals is approximately 50%.

TREATMENT

- When mild to moderate bleeding occurs,
- levels of factor VIII or factor IX must be raised to hemostatic levels in the 35-50% range. For life-threatening or major hemorrhages,
- the dose should aim to achieve levels of 100 % activity.

- Dose of FVIII (IU) = % desired (rise in FVIII) x Body weight (kg) x 0.5
- Dose of FIX (lU) =% desired (rise in plasma FIX) x Body weight (kg) x 1.4
- prophylaxis
- Desmopressin acetate (Stimate)

FACTOR XI DEFICIENCY(HEMOPH. C)

- The bleeding tendency is not as severe as in factor VIII or factor IX deficiency.

DEFICIENCIES OF THE CONTACT FACTORS (NONBLEEDING DISORDERS)

- (factor XII, prekallikrein, and
- high molecular weight kininogen)
- causes prolonged PIT, but no bleeding symptoms.

FACTOR VII DEFICIENCY

- prolonged PT but normal PTT.
- spontaneous intracranial hemorrhage
- and frequent mucocutaneous bleeding.

FIBRINOGEN DEFICIENCY (FACTOR I)

- prolongation of PT and PTT,
- thrombin time is prolonged.

FACTOR XIII DEFICIENCY

- symptoms of delayed hemorrhage are
- secondary to instability of the clot.
- mild bruising, delayed separation of
- the umbilical stump beyond 4 wk, poor' wound healing, and recurrent spontaneous abortions in women.
- screening tests for hemostasis are normal
- 5 M urea