REVIEW ARTICLE

Diathesis Hemorrhagic, Coagulation and Fibrinolytic System

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ABSTRACT

Bleeding is one of the most common complaints when coming to the hospital which can be mild to life-threatening. The balance of the impaired hemostasis system allows for abnormal bleeding such as hemorrhagic diathesis. Balance between blood clotting and bleeding is always maintained in the body under normal physiology. The coagulation system stops existing bleeding with vasoconstricts of blood vessels and the formation of early platelet plugs, this blockage is strengthened by the presence of a cascade of coagulations to form stable and sturdy blockages. Once bleeding has stopped, the fibrinolytic pathway is initiated to dissolve the blood clot to restore normal blood flow. balance the coagulants, fibrinolytic and inhibitor systems, creating a perfect physiological balance. Hemostatic imbalance is a global problem that can lead to thrombosis or hemorrhage.

Introduction

Frequent abnormal bleeding such as nosebleeds, menorrhagia, or Prolonged coagulation function was found from 26% to 45% in the health services.[1] This condition can be a state of hemorrhagic diathesis, which is a pathological condition that arises due to physiologic abnormalities of hemostasis.[2] The hemostasis is an important system as a defense mechanism from bleeding.[3] This complex process is integrated to stop unwanted bleeding and at the same time it prevents the formation of unnecessary clumps.[4] Hemostasis is a complex process, maintained in a very balanced way interactions between blood vessels, platelets, plasma coagulation factors, and fibrinolytic proteins in the formation of and dissolution of blood clots. If this balance is disturbed, massive bleeding can occur caused of hypocoagulation state and it also trigger hypercoagulation forms thrombosis with all its complications.[5] A better understanding of the basic of hemostasis and fibrinolytic has a positive impact on the management of diathesis hemorrhagic. In this literature review will be submitted related to the coagulation and fibrinolysis system as a part of hemostasis system as well as explanations of diathesis hemorrhagic with clinical examples and managements.

Review

Hemostasis System

The body has a perfect mechanism to control bleeding when it injured. An understanding of these basic physiological processes is essential to aid in the identification and diagnosis of bleeding disorders and relies on the hemostasis system to maintain them.[6] Hemostasis, defined as mechanism to stop bleeding, comes from the Greek which haeme meaning blood and stasis meaning stop.[7] So, it keeps the blood steady free-flowing state and always trying maintain in physiological balance.[5]

Hemostasis allows an organism to blockage vascular damage, keep the blood in a liquid state, and remove blood clots after restoration of vascular integrity. This hemostasis includes the process of blood clotting, activation of tightly regulated platelets , as well as vascular repair activations. Once injured, the hemostatic system uses most vascular and extravascular receptors that work together with blood components to cover the damage inflicted on surrounding blood vessels and tissues.[8]

The coagulation process is under the inhibition control of several inhibitors that limit clot formation, thus avoiding the formation of excess thrombus. At the end of the day, the coagulation and activation of thrombocyte will be disabled by inhibitors circulating in the blood and proteolytic feedback loops.[8] This thrombohaemmorhagic balance is maintained in the body in complex interaction of coagulation, fibrinolytic system, platelets and also blood vessel walls. Some thrombogenic and antithrombin components are listed in Table 1.[7]

Table 1. Thrombogenic and anti-thrombogenic components in the body.[7]

Location	Thrombogenic	Anti-thrombogenic
Blood vessel walls	Endothelium	Heparin
	Tissue factor	Thrombomodulin
	Collagen	Tissue Plasminogen
Circulation	Platelet activator factor	Anti-thrombin
	Coagulant factor	C dan S Protein
	Prothrombin	Plasminogen
	Fibrinogen	
	Von Willebrand Factor	

A normal hemostatic response can be organized into six distinct important phases, which fall into the three main categories of hemostasis (Table 2).[9]

Table 2. Represents the mechanical pathway of three different types of hemostasis.[9]

Types of Hemostasis	Mekanism
Primary Hemostasis	Vasoconstriction
	Formation of platelet plug
Secundery Hemostasis	Coagulation cascade activation
	Fibrin Deposit and Stabilization
Tertiery Hemostasis	Destruction of fibrin clots
	Dependent on Plasminogen activation

Primary Hemostasis

Primary hemostasis is a complex interactions of of platelets, vessel walls, and adhesive proteins that lead to the formation of early platelet plugs in exposed endothelia blood vessels.[7,10] This system relies on the integrity of the vascular (endothelial and subendothelial) and the function of platelets (in quantity and quality). It consists of two phases, vasoconstriction of the vascular and activation of platelets.[9,11]

Injured endothelial will cause local vasoconstriction, thus restricting blood flow to the area. It started when platelets releases of von Willebrand factor (vWF), a large plasma glycoprotein made and stored in endothelial cells and megakaryocytes. Platelets and vWF will combine to form a plug at the injury site. Circulating VWF continues to bind with collagen, FVIII and also other endothelial substances, allowing platelet blockages to attach the injury area.[6]

Secunder Hemostasis

Secondary hemostasis aims for the conversion of dissolved fibrinogens into insoluble fibrin strands that will strengthen platelet aggregation formed in the primary hemostasis phase. The classically established two pathways, intrinsic and extrinsic. Intrinsic pathways are activated through exposed endothelial collagen, and extrinsic pathways are activated through tissue factors released by endothelial cells after external damage.[10] But this theory is no longer used. Current evidence supports the understanding that intrinsic pathways are not a parallel pathways, but that in the process it will increase the thrombin products mainly initiated by extrinsic pathways. The latest model of coagulation system consists of 4 stages, including:12

1. Initiation Phase

At this stage, active coagulant factors are formed in small amounts.[8] When a blood vessel is exposed to a cell that expresses tissue factor on its surface, the coagulation system begins. Tissue factor (TF) - FVIIa complex acts as an initiation step on the damaged endothelium. TF binds to FVIIa in circulation, and at the beginning of FV, converts FIX to FIXa and FX into FXa. The coagulation process is also regulated by antithrombin inhibitors, tissue factor pathway inhibitors (TFPI) and C proteins (activated).[12] Activation of FIX by this TF-FVIIa complex serves as a bridge between classical and intrinsic extrinsic pathways, (Figure 1a and 1b).[7] Then, factor Xa binds to prothrombin to produce small amounts of thrombin that are not enough to produce fibrin, and also it is not strong enough that can be effectively stopped by tissue factor pathway inhibitors (TFPI).[12]

2. Amplification Phase

Because of not enough thrombin to convert fibrinogen to fibrin, positive feedback loop on the platelet surface, allowing for further platelet activation and clotting factors. During this process, platelets are covered in clotting factors that will be activated in readiness for the propagation process. The trombin produced, activates FV and FVIII which serves as a cofactor in the next propagation phase (Figure 2).[12]

3. Propagation phase

FVII convert into FIXa (intrinsic tenase) and FVa into FXa (prothrombinase). The accumulated enzyme complex (tenase complex and prothrombinase complex) on the platelet surface forms more thrombin in large amounts (thrombin explosion) and triggers platelet activation.7,12

4. Stabilization Phase

The resulting thrombin converts fibrinogen into fibrin threads and activates FXIII (fibrin stabilizing factor). This process covalently connects dissolved fibrin monomers to form a stable polymer and provides strength and stability for fibrin to be inserted in platelet gaps. Thrombin also activates actinated trombin-fibrinolysis-inhibitors, which protect blood clots from fibrinolysis.[7,12]

The coagulation mechanism is a cascade. When each factor is activated, it will continue to form more activate factors in the next step. As it moves further, the concentration of that factor increases in the blood.[10] In intact and healthy blood vessels, this cascade is not activated, and some anticoagulants play a role in inhibition of this mechanism. But when the vascular system is injured, blood is exposed to extravascular tissue rich in tissue factors , and cofactors for protease FVIIa.[13]

Coagulation is regulated and localized by several anticoagulant mechanisms. This mechanism prevents the formation of excess thrombus, which can lead to thrombosis. Thrombin formed not only acts as an anticoagulant, but also as a negative feedback function by activating plasminogen

into plasmin and stimulating antithrombin (AT) production. Plasmin works in the fibrin net and deciphers it. Some existing anticoagulants are Antithrombin (AT), TF Pathway Inhibitor (TFPI), Protein C (APC).[14]

Fibrinolysis

Fibrinolysis is a parallel system that is activated simultaneously with a cascade of coagulation and serves to localize and limit the formation of blood clots.[7] This occurs during the wound healing process and prevents blood clots in healthy blood vessels. This system works by activating proteolytic cascades that operate through the activation of plasminogen and plasmin proteolysis, it helps in clearing the injured and obstructed vessels, regenerating blood flow that is directed to the normal blood flow pathway.[9] Fibrinolysis is an enzymatic process that dissolves fibrin clumps into a product of fibrin degradation (FDP) by plasmin derived from plasminogen bound to the liver fibrin. The process of fibrinolysis consists of, formation of plasmin by plasminogen activators, and degradation of fibrin by plasmin.[15] There are two physiological activation pathways, involving plasminogens (tissue plasminogen activators; t-PA) and involves FXIIa (Hemagen) in which FXIIa converts prekallikrein to kalikrein, then kelikrein converts plasminogen to plasmin (Figure 3).[16]

Plasmin is strictly regulated by its inhibitors, such as Plasminogen Activator Inhibitor type 1(PAI-I), (α-2 antiplasmin) and TAFI thus preventing over-fibrinolysis.[17]

Diathesis Hemorrhagic

Diathesis hemorrhagic is a bleeding disorders tendency due to abnormalities in the hemostasis system.[2] The balance between clotting and bleeding is always maintained in the body under normal physiology. But any pathological scenario will tilt this balance for the occurrence of hemorrhagic or thrombotic complications. Hence as a hemostasis abnormality can occur categorized into those that cause abnormal bleeding and that cause abnormal clotting (table 3).[7] In general bleeding disorders can be caused by impaired vascular integrity, platelet disorders (number and function), and abnormalities of the coagulation system. These can result in a bleeding problem which may be inherited or acquired.[18]

Impaired vascular integrity

Vascular wall disorders can cause hemorrhagic symptoms. Bleeding is usually easy breakage, with consequent bleeding of small vessels (arterioles and capillaries), vascular purples enrolled usually minor bleeding in the skin, but the coagulation tests and platelet count are usually normal. Vascular fragility tests are a way to see if there are abnormalities.[18]

Vit C is one of the substances that are important in maintaining vascular integrity, by synthesis of hydroxyproline, an important collagen constituent. Collagen type IV is the main constituent of blood vessel walls, skin, and specifically, the basement membrane zone separating the epidermis from the dermis. One of the first clinical signs is petechiae bleeding in the hair follicles and purpura at the back of the lower extremities that fuse to form ecchymosis. Bleeding can occur in muscles, joints, nail pads, and gingiva tissue.[19] Impaired vascular integrity can occur "acquired" such as thrush due to water soluble vitamin C deficiency, infection and other inflammatory disorders such as Schönlein Henoch or anaphylactoid purpura, amyloidosis, and cryoglobulinemia. While the causes of vascular integrity disorders that are "hereditary" include Rendu-Osler-Weber syndrome, perioral nodules and intraoral angiomatoses or telangiectasis.[18]

Platelet disorders

Platelet disorders can be divided into two categories based on etiology, congenital and acquired and divided into two additional categories based on type, thrombocytopenic and thrombocytopathy.[20] Thrombocytopenia occurs when platelet count is reduced and is caused by one of three mechanisms: decreased production in the bone marrow, increased sequestration in the spleen, or accelerated destruction.[5] Thrombocytopathy, or qualitative platelet abnormality, can result from a defect in one of three critical platelet reactions: adhesion, aggregation, or granule release. Dysfunctional platelet mechanisms can occur in isolated disorders or in conjunction with dysfunctional coagulation mechanisms.[21] Some examples of congenital platelet disorders is Glanzmann thrombasthenia, which is consistent with abnormal αIIbβ3 leading to impaired platelet aggregation.[22] While two of the most common platelet disorders are idiopathic thrombocytopenia purpura (ITP) and thrombotic thrombocytopenia purpura (TTP).[23] ITP is an acquired hematologic disorder caused by immune-mediated destruction of platelets, and TTP caused by an acquired autoantibody that leads to decreased activity of the von Willebrand factor-cleaving protease ADAMTS13 that results in hemolytic anemia and severe thrombocytopenia.[24] Symptoms appear related to the severity and number of platelets, in mild case (platelet counts less then 20 x 109/L) petechiae and purpura may appear, in more severe cases (platelet counts less then 10 x 109/L) mucous bleeding can occur in the oral cavity, gastrointestinal and genitourinary tracts . Intracerebral hemorrhage, although rare, is the most common cause of death. However, most ITP patients are asymptomatic in the presence of platelet counts greater than 50x109/L.[25]

Thrombocytopenia can occur as a result of a manifestation of a particular disease, such as immune reaction in SLE, HIV, critical ill, viral or bacterial infection and other immune system suppression condition.[26] Thrombocytopenia can also be caused by hematological disorders such as Myelodysplasia, aplastic anemia, or leukemia, bone marrow suppression after cytotoxic chemotherapy therapy. The use of certain therapies such as antiplatelets such as heparin may also play a role in platelet function.[18]

Coagulation Function Disorder

Coagulation disorders can be congenital conditions or acquired because of drugs or disease processes. It can result of important coagulation factors or vWF deficiency. Bleeding manifestation from mild to severe, depending on the specific clotting factor affected and the degree of coagulation factor deficiency. Some examples of congenital coagulation disfunction are Hemophilia A due to VIII deficiency and Hemophilia B due to factor IX deficiency.[22]

The acquired disruption of coagulation function due to a disease process or the use of certain drugs, such as:

- Coagulation disorders in liver disease due to the deviation of vitamin K coagulation-dependent factors and procoagulant factors deficiencies (fibrinogen, prothrom¬bin and factors V, VII, IX, X, XI and XII are synthesized in the liver).[27]
- Kidney disorders accompanied by uremia has a high risk of bleeding due to impaired coagulation function.

In Chronic Kidney Disease (CKD) patients manifest a coagulopathy consisting of delayed clot formation with increased final clot strength and decreased clot breakdown when compared to healthy patients.[28]

- History of therapy with heparin as a strong anticoagulant that binds with antithrombin III strongly inhibit the activation of FIX, FX, and FXI, thereby reducing the formation of thrombin and fibrin.[20]
- Critical illness conditions such as Disseminated intravascular coagulation (DIC) cause prolongation of coagulation function, PT and aPTT values increase significantly during infection,[29] which is characterized by systemic activation of blood coagulation generation and deposition of fibrin, leading to microvascular thrombi in various organs and contributing to multiple organ dysfunction syndrome (MODS). Consumption of clotting factors and platelets in DIC can result in life-threatening hemorrhage.[30]

Diathesis hemorrhagic has many etiologies, it is important to know as quickly and accurately in order to give the best management. The type of bleeding symptom can be differentiated between a coagulation factor disorder and a platelet disorder (Table 4).[31]

Bleeding History

The history focuses on bleeding symptoms (particularly mucocutaneous, internal tissue, and bleeding related to the procedure), a history of bleeding in the family, and the medications. Important Comorbidities history is important to consider include liver, kidney, and sepsis diseases that cause bleeding. Bleeding assessment tool (BAT) can help to standardize the approach to bleeding history.[32]

The BAT system precisely describes the severity of symptoms, informs treatment, and may predict the risk of future bleeding. BAT MCMDM-1 is used in patients with suspected Von Willebrand disease, and BAT-ISTH for other cases.33 The ISTH-BAT score is one of the tools to predict the presence of bleeding disorders, a history of mucocutaneous bleeding by analyzing 14 specific bleeding symptoms and assessing each symptom on a scale of 0 to 4. The normal range for the total score is 0-3 for adult men, 0-5 for adult women and 0-2 in children for men and women and the limit for positive or abnormal BS is 4 in adult men., 6 in adult women and 3 in children.[33]

Physical examination

The physical examination should be focus on confirming and assessing the severity of the bleeding and eliminate other possible structural causes. It helps guiding the urgency for the treatment of bleeding quickly and appropriately. Examination focuses on signs of bleeding in mucocutaneous, deep tissue or joint bleeding as well as assessing structural lesions that may contribute to bleeding symptoms.[32]

A thorough physical examination can provide a lot of information related to the etiology of bleeding. Hemophilia or bleeding due to other congenital abnormalities should be considered in patients with a history of spontaneous hemarthrosis, muscle hemorrhage, or retroperitoneal hemorrhage. Mucocutaneous bleeding (petechiae, epistaxis, gingival, gastrointestinal, or genitourinary hemorrhage) indicates the possibility of platelet abnormalities. Hepatomegaly indicates liver failure, while splenomegaly may suspect malignancy. Although very rare, splenomegaly can be a sign of idiopathic thrombocytopenia purpura (ITP).[1]

Laboratory approach

A person with a history of either minor or massive bleeding, Initial laboratory evaluation is generally carried out to determine the underlying cause. coagulation test, especially PT and aPTT have more sensitivity in cases of bleeding supported by other tests. Because prolongation of the aPTT or PT may indicate an acquired or congenital clotting factor deficiency or an inhibitor of one or more coagulation factors.[23] Other initial laboratory tests should include a complete blood count (CBC) to assess thrombocytopenia, liver and kidney function tests, and fibrinogen exclude DIC or hypofibrinogenemia.[32] In addition, the examination of bleeding time and removal of peripheral blood removal when needed.[23] The investigation of the bleeding problem should be as methodical as possible. Figure 4 shows a flow chart for the interpretation of the coagulation abnormality test result.[34]

Management

The primary focus in the treatment of clinically relevant hemorrhagic disorders should be directed at the appropriate management of the underlying disorder. It is important to making a correct diagnosis of the underlying etiology. Besides giving the proper treatment for underlying disorders, proper preventive care, a supportive treatments are also needed to correct coagulation defects.[23]

The management of patients with hemorrhagic diathesis is aimed at reversible defect correction, prevention of hemorrhagic episodes, immediate control of bleeding as it occurs, and management of the sequelae of the disease and its therapy.[34] Principal agents for systemic management of patients with bleeding disorders shows in table 5.[35]

Table 3. Classification of coagulation disorders.[7]

Bleeding Disorders	Thrombotic System Disorder (Thrombophilia)
Hereditary	Hereditary
Von Willebrand Disease	Thrombofillia herediter
Haemophilia A	Antithrombin III Deficiency
Haemophilia B	Protein C Deficiency
Haemophilia C	Protein S Deficiency
FV Deficiency	Factor V Leiden (FV Mutation)
FVII Deficiency	
FXIII Deficiency	
Protrombin Deficiency	
Afibrinogenemia	
Acquired	Acquired
Consumptive coagulopathies	Antiphosfolipid Antibody Syndrome
DIC	DIC that increases levels of factors VIII, IX, XI, or fibrinogen
Microangiopathic haemolytic anemias	Fibrinolisis Defect
Vitamin K Deficiency	Homozygous homocystinura
Liver disease	

Table 4. Clinical differences diathesis hemorrhagic[31]

Clinical symptoms	Defects in coagulation disorder	Platelet disorders
Gender	80 – 90% Male	Equal
Onset of bleeding (after trauma)	Delayed	Spontaneous or immediately
Mucosal bleeding	Rare	Common
Petechiae	Rare	Characteristic
Ecchymoses	Large and solitary	Small and multiple
Hemarthrosis	Characteristic	Rare
Bleeding small cut	Minimal	Persistent

Table 5. Primary agent for systemic management of patients with bleeding disorders.[35]

Agent	Common Indication
Platelet	Platelet count < 10,000 in nonbleeding individuals as a Prophylactic transfusion , < 50,000 presurgical level or minor invasive procedures , > 50,000 in actively bleeding individuals, Nondestructive thrombocytopenia
Fresh Frozen Plasma	Undiagnosed bleeding disorder with active bleeding, Severe liver disease, When transfusing > 10 units of blood, Immune globulin deficiency
Cryoprecipitate	Fibrinogen deficiency, Hemophilia A, von Willebrand's disease when factor concentrates and DDAVP are unavailable,
FVIII concentrate	Hemophilia A with active bleeding or pre-surgery; some cases of von Willebrand's disease
FIX concentrate	Hemophilia B, with active bleeding or pre-surgery, Prothrombin complex concentrates used for hemophilia A with inhibitor
Desmopressin	As antifibrinolytics for inherited platelet function disorders, particularly storage pool defects, or in patients with uremia
Epsilon-aminocaproic acid	Adjunct to support clot formation for any bleeding disorder
Tranexamic acid	Adjunct to support clot formation for any bleeding disorder

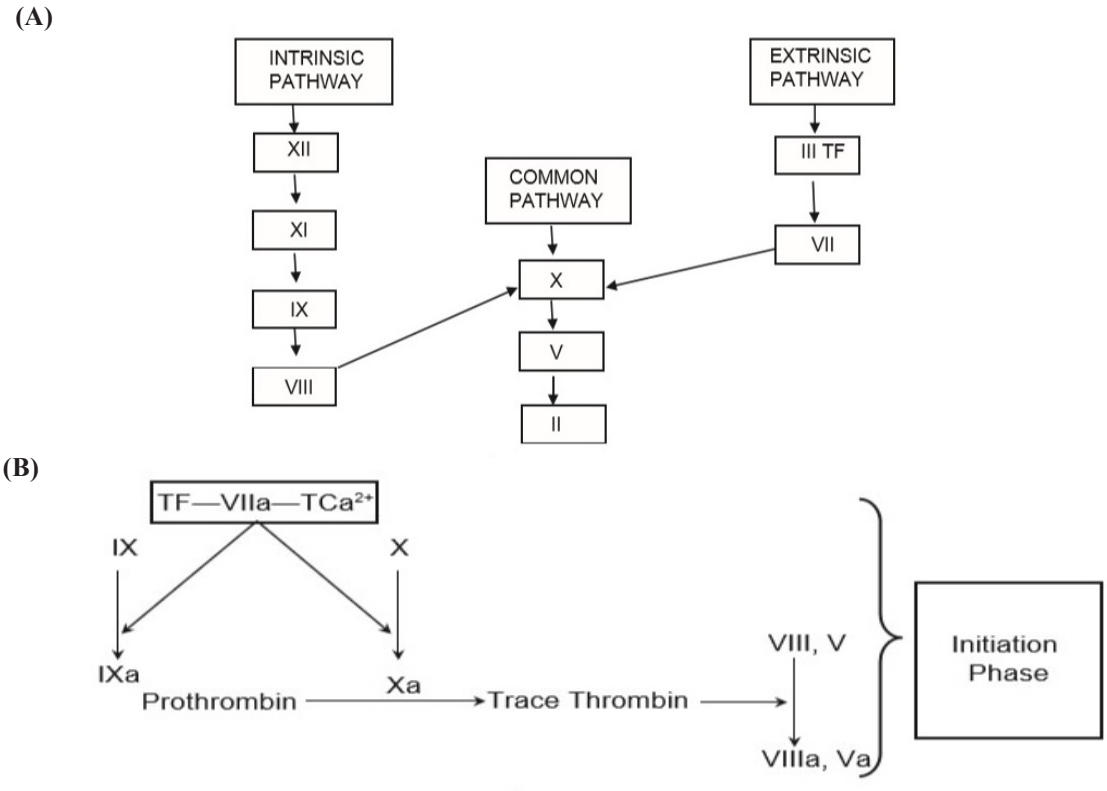

Figure 1. (A) Old concept of coagulation system.[7] ; (B) New concept of coagulation system. (Initiation phase)[7]

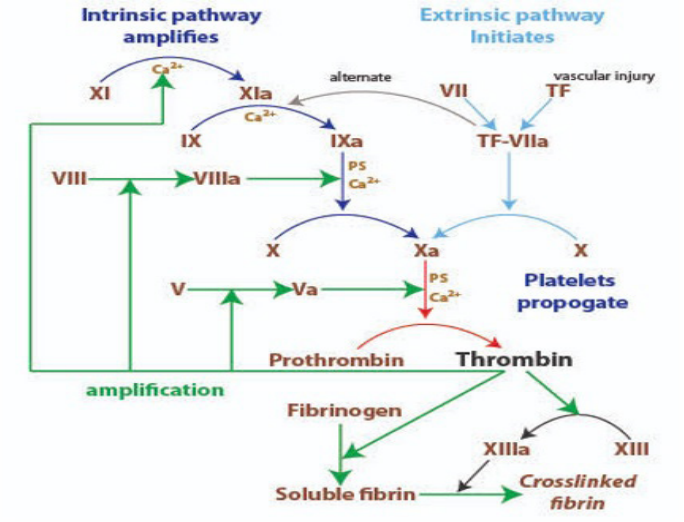

Figure 2. Schematic of the coagulation cascade which leads to the formation of thrombin (initiation phase) and continued with the amplification phase as a positive feedback loop and propagation to form larger amounts of trombin. Its stabilized the plug and convert a dissolved fibrinogens into insoluble fibrin strands.[12]

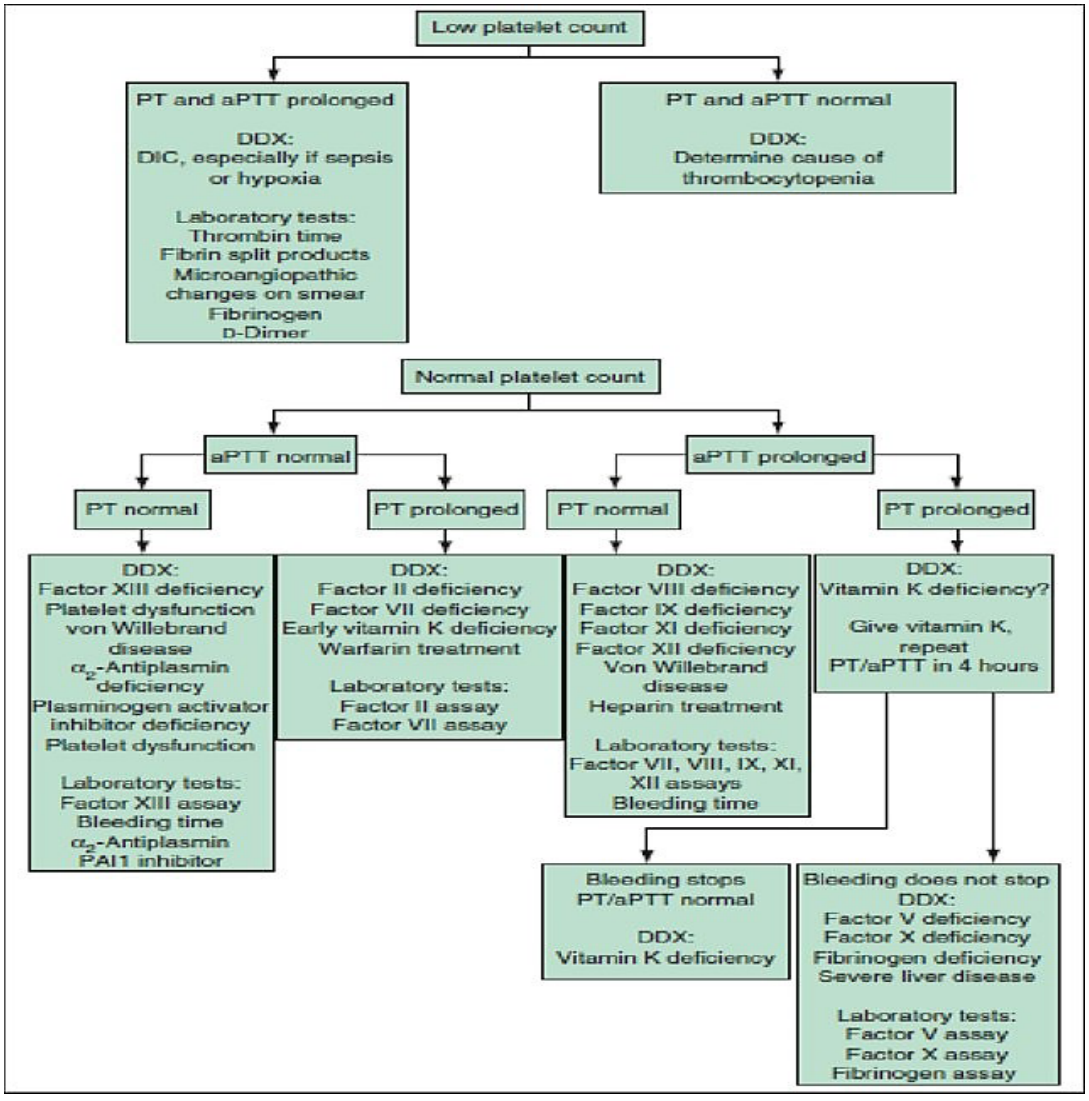

Figure 3. The management of patients with hemorrhagic diathesis

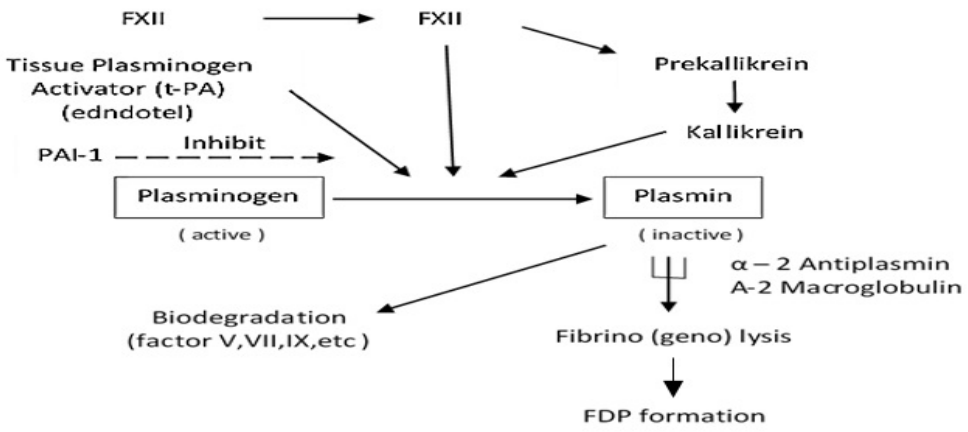

Figure 4. Physiology of Fibrinolysis System [16]

Conclusion

An understanding of hemostasis and fibrinolysis as the basis for abnormalities in hemorrhagic diathesis conditions is very important. The hemostasis process consists of several stages that run in a balance between the coagulation and fibrinolysis systems which are maintained in a balanced condition to prevent bleeding or thrombosis complications. A thorough identification of the history of the disease, medication, physical examination, and a good investigation helps in proper treatment according to the underlying etiology.

Recommendations for clinical practice, disorders of fibrinolysis should not be routinely tested for patients with a bleeding tendency, because they are rare and laboratory diagnostics unreliable. Fibrinolysis assays should be undertaken in a specialized laboratory when there is a high index of suspicion, raised by: recurrent abnormal bleeding, mainly delayed bleeding post-trauma/surgery and mucocutaneous bleeding positive family history of an established hyperfibrinolytic disorder co-occurrence with reproductive failure unusual bleeding sites (e.g. intramedullary hematomas or umbilical cord bleeding). In the future, diagnostics may be improved by the implementation of thrombin and plasmin generation assays and genetic tests using next-generation sequencing.

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Conflict of Interest

The authors indicate no potential conflicts of interest.

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