CLINICAL APPROACH TO THE BLEEDING PATIENT

Introduction

Disorders of hemostasis can be divided into problems secondary to platelets, the vessel wall, or the coagulation cascade. When initially investigating bleeding problems in a patient, it is helpful to separate out the differential by:

1. quantitative platelet disorder
2. qualitative platelet disorder
3. coagulation disorder—quantity impaired due to failure of production, or consumption
4. coagulation disorder—activity impaired due to genetic abnormality in clotting factor(s) or acquired inhibition.

The summation below is derived from Robert I. Handin’s chapters on coagulation in Harrison's Textbook of Medicine (14th edition, chapters 117, 118), the American Society of Hematology self assessment program and Robbins Basic Pathology.

Disorders of the Platelet and Vessel Wall

Platelet disorders

Normally, platelets arise from the fragmentation of megakaryocytes. They circulate, with approximately 1/3 sequestered in the spleen at any one time. The life span is approximately 7-10 days. They are removed from circulation by phagocytosis. Stimulation of additional platelets production is via thrombopoietin.

Platelet count varies by the patient's nutritional state, menstrual cycle, and is considered one of the body’s acute phase reactants. Secondary or reactive thrombocytosis can occur in systemic infection, tumors, bleeding, and mild iron deficiency. Primary thrombocytosis can occur in hematologic tumors such as myeloproliferative disorders.

Thrombocytopenia

Thrombocytopenia is normally caused by decreased bone marrow production, increased splenic sequestration, or accelerated destruction of platelets. Examination of the peripheral blood smear can help determine the cause. Sometimes a bone marrow biopsy is necessary. A key part of the physical exam is assessment of spleen size.

When a patient presents with a low platelet count and an enlarged spleen, one needs to consider whether or not the spleen size is due to systemic illness, like liver disease, storage disease, tumor, or congestive splenomegaly. If the splenomegaly cannot be explained, then additional investigation for hematologic disorders needs to be undertaken.
When a patient presents with a low platelet count and a normal spleen, one needs to verify that there are no signals of abnormal marrow production. One needs to consider excess destruction, because of immune mediated processes, medications, or systemic problems like sepsis, DIC, and vasculitis.

**Impaired production**

Normally, production disorders effect more than the megakaryocytic cell line, so a patient will also have anemia or leukopenia. The most common causes of decreased platelet production are marrow aplasia, fibrosis, or infiltration with other neoplastic cells. Chemotherapy drugs used for cancer treatment, immunosuppression, and occasionally rheumatologic disorders, can also impair megakaryocytic proliferation and maturation. There are rare congenital disorders in which megakaryocytes are absent.

**Splenic sequestration**

At any one time, about a third of the platelets are sequestered in the spleen. Splenectomy will increase the platelet count by about 30%. But if the spleen is enlarged, an increased percentage of platelets will be removed from circulation. Commonly, portal hypertension from liver disease, splenic infiltration by lymphoma, or myeloproliferative disorders will cause splenic sequestration of platelets to increase. Splenomegaly can also occur because of chronic hemolytic diseases, or heart failure.

**Accelerated destruction**

Non immunologic thrombocytopenia can arise when there is fibrin thrombi, intravascular prosthesis, or abnormal vessels. Conditions such as HUS/TTP and DIC, are examples of thrombocytopenia due to increased destruction of platelets.

Patients can also have immunological destruction of platelets. This occurs during some viral or bacterial infections, after the administration of certain drugs, and in the disorder called ITP.

**Drug-induced thrombocytopenia**

Many common drugs caused thrombocytopenia. These include myelosuppressive drugs like chemotherapy agents, thiazide diuretics, alcohol, and estrogens. There are also drugs that can cause immunologic platelet destruction such as antibiotics, certain sedatives, or even some foods. When the cause is immunologic, the platelet is damaged by compliment activation. The most common cause of thrombocytopenia in hospitalized patients is heparin. About 10-15% of patients receiving heparin -- including low molecular weight heparin--develop thrombocytopenia. This can be devastating. It is due to drug-antibody binding to
platelets, or to direct platelet agglutination by heparin. Prompt cessation of heparin is essential, and anticoagulation with an alternative agent is necessary in many cases. A full review of medications is an essential part of working up any patient with thrombocytopenia.

**Idiopathic thrombocytopenic purpura**

A typical presentation of ITP is an otherwise healthy individual who has a rapid development of severe thrombocytopenia. Often these individuals will not have bleeding problems, but will have some bruising. The diagnosis of autoimmune thrombocytopenia is a diagnosis of exclusion. One can make this in patients who have a low platelet count and no other hematologic disorders, viral infections, splenomegaly, or medication interactions. Bone marrow aspirate is generally not needed—but is recommended in patients over the age of 60 as they may have an unrecognized neoplasia or myelodysplastic disorder.

In some patients, platelet antibodies can be detected, but this is not necessary to confirm the diagnosis. In a patient with isolated thrombocytopenia and no other hematologic abnormality, the diagnosis of other severe hematologic disorders—such as leukemia or bone marrow failure is unlikely.

Severe thrombocytopenia following a viral infection or upper respiratory illness is common in children and accounts for about 90% of pediatric ITP. Occasionally one can also see ITP with mononucleosis, toxoplasmosis, CMV infection and HIV.

In adults, ITP is typically chronic. The presentation is an abrupt fall in platelet count and patients may have a new history of bruising, bleeding, or menorrhagia. Chronic ITP is due to antibodies directed against the glycoprotein IIb IIIa or glycoprotein IB-IX complex. It is important to rule out lupus or any other signs and symptoms of rheumatologic disorder, lymphoma, and infection, including HIV. It is also essential to look at the peripheral blood smear and ensure there are no abnormalities that could be related to a microangiopathic hemolytic anemia.

Treatment of ITP is with steroids, splenectomy, immune suppression, or, in some refractory cases the initiation of recombinant thrombopoietin.

**Functional Platelet Disorders**

Platelets need to be able to adhere, aggregate and release their granules for hemostasis to occur. Functional platelet disorders which arise from a problem of adhesion include Bernard-Soulier disease and von Willebrand's disease. Uremia, in the setting of renal failure also impairs platelet adhesion. Disorders of aggregation include Glanzmann's thrombasthenia and inherited disorders of fibrinogen. Medications may also impair platelet aggregation, for example IIb-IIIa inhibitors. There are rare inherited
abnormalities of platelet granules, the more common problems are acquired--i.e. coronary bypass, myeloproliferative disorders, and nonsteroidal anti-inflammatory agents.

**Von Willebrand's Disease**

This is the most common inherited bleeding disorder, and occurs in about 1/800-1000 people. Von Willebrand's factor is a multimeric plasma glycoprotein which functions to help platelets adhere by linking them to the vascular wall and endothelium. It also is the carrier protein for factor VIII, a critical blood coagulation protein. Different parts of the von Willebrand's subunit contribute to these functions. A decrease in plasma von Willebrand concentration or loss of the high molecular weight multimers decrease the platelet adhesion and can cause clinical bleeding.

Von Willebrand disease (VWD) is a group of genetically heterogenous disorders resulting in abnormal function of the Von Willebrand factor (VWF). More than 100 mutations have been described. Symptoms include mucocutaneous bleeding (epistaxis, easy bruising, prolonged bleeding after minor trauma, menorrhagia and gastrointestinal bleeding) of varying severity. Hemarthrosis is relatively rare - unlike hemophilia, the mode of inheritance is predominantly autosomal dominant (some autosomal recessive variants have been described). Although it is the most common inherited disorder of coagulation with a prevalence of 1-2%, only a small fraction of individuals inheriting the gene suffer from a clinically significant diathesis.

This disease is clinically heterogeneous. In mild cases, bleeding occurs only after surgery or trauma. However, some individuals can have spontaneous nosebleeds, or gastrointestinal, genitourinary, or oral bleeding. Laboratory workup is important. The most diagnostic pattern is the combination of a prolonged bleeding time, a reduction in the plasma von Willebrand's factor concentration, reduction in ristocetin cofactor activity, and reduced factor VIII activity.

Since currently available screening tests (PTT and bleeding time) are non-specific and not highly sensitive, in the presence of clinical symptoms, specific tests including quantitative assay (VWF AG), functional assay (VWF ristocetin cofactor/ collagen binding capacity), structural analysis (multimer gel analysis), platelet count and plasma levels of factor VIII are recommended.

However, there is variability in these tests. The levels of von Willebrand's factor can be influenced by blood type group, central nervous system disorders, inflammation, and pregnancy.

Several different mutations in the Von Willebrand factor gene lead to quantitative and qualitative changes in the von Willebrand factor. Different management strategies in the various types of VWD underlie the importance of classification.
Traditionally, the disease is phenotypically classified into three broad categories:

- Type 1 (partial quantitative deficiency, most common type)
- Type 2 (qualitative defect)
- Type 3 (total deficiency)

Based on specific structural abnormalities, type 2 VWD has been further subdivided into four subtypes (2A, 2B, 2M, 2N).

<table>
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<tr>
<th>Type I disease.</th>
<th>This is the most common abnormality. Individuals have a mild to moderate decrease in plasma von Willebrand's factor.</th>
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<tr>
<td>Type II disease.</td>
<td>This is much less common. In these cases there are normal or near normal levels of protein—but there are qualitative abnormalities. There are a number of subtypes of type II disease.</td>
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<td>Type III disease.</td>
<td>There are very few individuals born with type III disease. These individuals may be either a double heterozygote, or homozygous for a single defect in von Willebrand's factor. These patients have severe mucosal bleeding, no detectable von Willebrand's factor antigen or activity, and may have very little factor VIII.</td>
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Treating von Willebrand's disease can be complex. One may use cryoprecipitate which is the fraction of plasma that is in rich in von Willebrand's factor. There is also recombinant therapy. One of the most effective treatments is the use of DDAVP, which raises the plasma von Willebrand's factor level in normal individuals in patients with type I disease. The therapeutic strategies depend on accurate diagnosis and subtyping of VWD. A clinical trial with DDAVP is recommended for increasing endogenous VWF in type 1 disease, although the response is variable. Type 3 patients are unresponsive to DDAVP and exogenous VWF is the treatment of choice.

In patients with type 2 disease, DDAVP is not always effective. Specifically, in type 2B, DDAVP may worsen the thrombocytopenia and also cause spontaneous platelet aggregation (although no cases of thrombosis have been reported). Thus treatment with VWF concentrates is required for maintaining hemostasis in most type 2 VWD.

In summary, the diagnosis of VWD may be difficult as the screening tests (APTT and/or bleeding time) may be normal or only marginally prolonged. Distinguishing the variants is also challenging and necessary as the management strategies differ.
Platelet membrane defects

There are two rare but well-defined platelet defects. These defects are characterized by a loss or a defect in glycoprotein receptors. The receptors to the glycoprotein 1B/2A and the glycoprotein 2B3A complex. Patients with Bernard Soulier syndrome have decreased platelet adhesion because the glycoprotein 1B/2A complex is deficient or dysfunctional. In individuals with Glanzmann's disease, patients have a defect in the glycoprotein 2B3A complex. Both disorders are autosomal recessive. They are characterized by impaired hemostasis and recurrent episodes of severe mucosal bleeding. They are diagnosed using platelet aggregation studies.

Platelet release defects.

The ingestion of aspirin and nonsteroidal drugs inhibit platelet production of Thromboxane A2, which is an important mediator of platelet secretion and aggregation. A single dose of aspirin will impair hemostasis for 5-7 days. Platelets that have been impaired with aspirin generally produce minimal symptoms such as easy bruising and bleeding. The antiplatelet effect of drugs such as aspirin is more dramatic when there administered to patients with underlying defects like von Willebrand's disease or hemophilia. Patients who have taken aspirin should be treated as if they have a mild bleeding deficiency for the next 5-7 days.

There are also systemic disorders that can impair platelet function. Uremic platelet dysfunction is clinically the most important. It is not understood how uremia impairs platelet function, however, there is a good correlation between the degree of uremia and bleeding symptoms. Bleeding can usually be reversed by dialysis.

Storage pool defects

Patients with defective platelet granules can have a mild bleeding disorder. These are rare and maybe an inherited disorder or part of the systemic condition. Again the characteristics are easy bruising mucosal bleeding and prolonged bleeding time.

Vessel wall disorders

Bleeding from vascular disorders is called thrombotic thrombocytopenic purpura. It is usually mild and confined to the skin and mucous membranes. Vascular purpura arises from damage to the capillary endothelium, abnormalities in the vascular subendothelial matrix, or the formation of abnormal blood vessels. There are also several disorders which involved the vessel wall and can contribute to more severe bleeding in organ dysfunction.
Thrombotic thrombocytopenic purpura

TTP is an aggressive, often lethal disorder. It is initiated by endothelial injury, and subsequent release of von Willebrand's factor and other procoagulant materials from the endothelium. Contributing also is a circulating protein which induces platelet aggregation, and which blocks the cleavage of von Willebrand's factor into appropriate subunits. Individuals with TTP developed a severe Coombs negative hemolytic anemia with schistocytes and damaged red cell fragments notable on the blood smear. They also have thrombocytopenia, but do not have a DIC type picture. Vasculitis can make TTP more likely. Treatment is with plasmapheresis. It often requires multiple treatments for control. Related to TTP is the **hemolytic uremic syndrome**. In this condition onset is preceded by a febrile or viral illness and an infectious or immune complex mediated cascade of events then provokes the endothelial injury. In HUS, the disease can remain localized to the kidneys. Individuals can require dialysis.

Henoch-Schönlein purpura

This is a distinct self-limited vasculitis which occurs in children in young adults. Patients have an acute inflammatory reaction in both the capillaries and small arterioles. Patient's developed a purpuric rash, polyarthralgias, and hematuria. And all coagulation tests are normal. Some patients may develop acute renal failure, chronic nephritis as well as colicky abdominal pain.

Febrile illnesses

A number of acute febrile illnesses cause capillary fragility and skin bleeding. For example Rocky Mountain spotted fever includes a pathogen which damages endothelial cells. Thrombocytopenia is a frequent finding in acute infectious disorders and may contribute to skin bleeding. In addition whenever the platelet count falls below 10,000 per microliter, gaps between the endothelial cells allow the exiting of red cells into the dermis leading to the formation of petechiae.

Increased immunoglobulin conditions

Occasionally patients with diffuse polyclonal hypergammaglobulinemia will develop purpuric lesions on the lower limbs—a benign condition called hypergammaglobulinemia purpura. Vascular purpura may occur in patients with monoclonal plasma protein abnormalities including Waldenström's and multiple myeloma. In the conditions, increased serum viscosity impairs blood flow through capillaries.
Scurvy

Patients with vitamin C deficiency develop scurvy. This can include painful episodes of skin bleeding, bleeding into muscles, gastrointestinal and genitourinary bleeding. Vitamin C is needed to synthesize an essential constituent of collagen.

Medications

Patients with Cushing's syndrome characterized by an excess production of glucocorticoids, or patients on large doses of glucocorticoids, developed generalized protein wasting and may show skin bleeding easy bruising due to atrophy of the supportive connective tissue. There is also a condition called senile purpura were patients develop atrophy of the perivascular connective tissue due to aging.

Disorders of coagulation

Patients with plasma coagulation defects characteristically bleed into muscles, joints, and body cavities hours or days after an injury. There are inherited coagulation disorders, most of which are due to defects in single coagulation proteins. Factor VIII and factor IX deficiency constitute majority of congenital coagulation disorders, and are inherited in and X-linked manner. These disorders prolonged either the prothrombin time (PT), the partial thromboplastin time (PTT), or both these important laboratory screening tests. If they are abnormal, assays of specific coagulation proteins are then carried out using the PT or PTT tests with plasma from congenitally deficient individuals as a substrate. The corrected effects of these on the patient plasma are measured and expressed as a percentage of normal pool plasma standard. The interval range for most coagulation factors is from 50-100% of this average value, and the minimal level of most individual factors needed for adequate hemostasis is about 25%.

Acquired coagulation disorders are more frequent, and more complex. They arise from deficiencies of multiple coagulation proteins and affect both primary and secondary hemostasis. The most common acquired hemorrhagic coagulation disorders are 1-- disseminated intravascular coagulation, 2-- hemorrhagic diathesis of liver disease and 3 -- vitamin K deficiencies and complications from anticoagulant therapy.

Factor VIII Deficiency--Hemophilia A

Factor VIII coagulant protein is a large single chain protein. It is synthesized in the liver parenchymal cells. It circulates complexed to the von Willebrand factor protein--this explains why individuals with deficient von Willebrand factor have low factor VIII levels. The factor VIII gene is located on the X chromosome. This means that the disorder is X-linked. One in 10,000 males is born with either a deficiency or dysfunction of the factor VIII molecule.
Hemophilia A is characterized by bleeding into soft tissues, muscles, and weightbearing joints. Normal hemostasis requires about 25% factor VIII activity; symptomatic patients usually have factor VIII levels below 5%.

Patients with less than 1% factor VIII activity had severe disease and bleed frequently without discernible trauma. Patient with levels between 1-5% have moderate disease and those with levels over 5% have mild disease. Hemophiliac bleeding occurs hours to days after injury, and it can involve any organ and may continue for days or weeks. This can result in large collections of partially clotted blood which can put pressure on adjacent normal tissues and cause necrosis of muscles, venous congestion, or ischemic damage to nerves. For example, hemophiliacs often developed femoral neuropathy due to pressure from unsuspected retroperitoneal hematomas. They can also develop large calcified masses of blood and inflammatory tissue that are occasionally mistaken for soft tissue sarcomas.

Diagnosis is often early in life. A typical hemophiliac patient may be diagnosed after circumcision, after falls as they learn to walk or crawl, or if they develop hemarthrosis as a young person. After a joint has been damaged by repeated bleeding episodes, there is articular cartilage damage, osteoarthritis, ankylosis and even muscle atrophy. Hematuria is also common. It is often self-limited, however. The most feared complications and hemophiliacs include oral pharyngeal bleeding requiring sometimes emergency intubation and CNS bleeding without antecedent trauma.

Diagnosis includes a platelet count, bleeding time, PT and PTT. Typically an individual with hemophilia A will have a prolonged PTT with all the other tests normal. Because of the clinical similarity of factor VIII deficiency and factor IX deficiency, any male with appropriate bleeding history and prolonged PTT should have assays for factor VIII and factor IX performed.

**Hemophiliac therapy**

Individuals with hemophilia require specialized care, and should be treated in tertiary care centers. Early treatment is more effective, less costly and can be lifesaving. It is critical to avoid the use of aspirin or aspirin containing drugs which impair platelet function and may cause severe hemorrhage. Repletion of factor VIII comes from plasma products enriched in factor VIII -- use of these prophylactically has, in general, reduced the degree of orthopedic deformity that these patients suffer. However, the use of pooled plasma to obtain factor VIII concentrates has also produced many of the serious complications of this disorder--including viral hepatitides, chronic liver disease, and HIV infection in patients receiving these factor concentrates. Recombinant factor VIII is now used-- which has markedly reduced the secondary viral infections these patients develop. Dosing of these recombinant factors can be complicated--and a specialist should be involved in treatment. It is also critical that these individuals are
routinely monitored for viral infections. They may also develop iron deficiency, hemolysis and inhibitors of factor VIII—which can provide a unique complication--has their body destroys the infused factor VIII. Patient should also receive genetic counseling and prenatal diagnosis should they desire it.

**Factor IX deficiency--hemophilia B**

Factor IX has also been mapped to the X chromosome and many patients with deletions and mutations in the factor IX chromosome have been described. This condition, also called Christmas disease, occurs in one and 100,000 male births, and although it is clinically indistinguishable from factor VIII deficiency it requires treatment with a different plasma fraction--making accurate diagnosis critical.

Factor XI deficiency is an inherited autosomal recessive trait and has been identified to occur somewhat more frequently among individuals of Ashkenazi Jewish descent. In contrast to hemophilia A, in hemophilia B the correlation between factor level and propensity to bleed is not as precise. There is less spontaneous bleeding, and hemarthroses are rare. It is treated with infusion of fresh plasma frozen plasma after traumas.

Factor VIII antibodies or an acquired factor VIII deficiency occasionally happen. These antibodies are associated with collagen vascular disease, some medications, including penicillins, but may also occur in individuals with no underlying abnormalities. Large, spontaneously developing hematomas are classic presentation. Helpful in defining this disorder is an activated partial thromboplastin time (APTT) mixing study.

**Other factor deficiencies**

There are also reported deficiencies of factor V, factor VII, factor X, and prothrombin factor--factor II. These are all exceedingly rare, and are autosomal recessive disorders. Spontaneous or posttraumatic musculoskeletal bleeding or menorrhagia can occur but hemarthroses are common. FFP is the appropriate therapy. Defects of the contact activation pathway, involving factor XII, high molecular weight kininogen, and prekallikrein can cause laboratory abnormalities but no clinical bleeding. Despite dramatic prolongation of the PTT--often greater than 100 seconds--deficient individuals have normal hemostasis and can go under undergo major surgery without plasma replacement therapy.

One can also have either deficiencies of fibrinogen or abnormal fibrinogen. Fibrinogen is necessary for the production of the fibrin monomer, which polymerizes to form a fibrin clot. Fibrinogen is needed for platelet aggregation and fibrin formation. However, patients with an absence of fibrinogen have infrequent, mild bleeding episodes. There also mutations that have been identified in fibrinogen. These can prevent appropriate polymerization of fibrin monomer.
The dysfibrinogenemias are almost always inherited as autosomal dominant trait. Patients have a slightly prolonged PT and PTT, a prolonged thrombin time, and there is disparity between the quantity of fibrinogen measured with functional and immunological assays. Most patients have no symptoms while others have moderate bleeding. Some patients with liver disease, end-stage HIV, and lymphoproliferative disorders developed an acquired form of fact dysfibrinogenemia.

**Vitamin K deficiency**

This is a fat-soluble vitamin. It plays a critical role in hemostasis. It is absorbed in the small intestine and stored in the liver. There are three causes a vitamin K deficiency--inadequate dietary intake, intestinal malabsorption, and loss of storage sites due to hepatocellular disease. Acutely ill patients can become deficient within 7-10 days. It is also seen in chronic liver disease, particularly primary biliary cirrhosis, and malabsorption states.

When vitamin K deficiency develops, plasma levels of all prothrombin complex proteins--factors II, VII, IX, X; protein C and protein S—decrease. Factor VII and protein C have the shortness half lives, and decreased first. Patients may have a preliminarily prolonged PT, but as the levels of the other factors fall, the PTT will also become prolonged period

Parenteral administration of vitamin K rapidly restores vitamin K levels of the liver and permits normal production of the prothrombin complex proteins.

**Iatrogenic Vitamin K deficiency from warfarin**

The administration of vitamin K is of course the most important antidote for reversal of an elevated INR in the setting of warfarin therapy. Not all patients with an elevated INR have complications, but one can certainly see severe bleeding if the INR is allowed to become elevated. Deciding the most appropriate therapy to reverse excessive warfarin anticoagulation can be challenging. The most important thing is to assess the risks of bleeding versus the risk of reversing anticoagulation. It is important to remember that if the patient is anticoagulated, there can be risks of blood clots if that anticoagulation is reversed. However, there is also risk of bleeding when the patient becomes over anticoagulated.

Vitamin K therapy is used to reverse over anticoagulation with warfarin. This makes sense, as warfarin blocks the vitamin K dependent clotting factors. Vitamin K overrides the warfarin blockade of the gamma carboxylation pathway and results in production of functional clotting factors within hours, if the liver is healthy. The dose of vitamin K determines how much of the warfarin effect will be reversed. A dose of 5 mg of vitamin K will significantly reverse the anticoagulation effect of warfarin within 12-24 hours. A 10 mg dose will usually block the warfarin effect completely and interfere with attempts to resume
anticoagulation with warfarin. The risk of clotting versus the risk of bleeding determines how much vitamin K check is and how long to withhold the warfarin dose.

Fresh frozen plasma is the most rapid way to replace vitamin K clotting factors and reverse the anticoagulation. However, because of the infectious and allergic risks associated with blood products, fresh frozen plasma is only used to reverse warfarin if the patient has a serious bleeding complication or excessive risk of bleeding.

Disseminated intravascular coagulation

This can be either explosive and life-threatening, or relatively mild and subclinical. DIC is most frequently associated with obstetric catastrophes, bacterial sepsis, metastatic malignancy, and massive trauma.

The clinical presentation varies with the stage and severity of the syndrome. Most patients have extensive skin and mucous membrane bleeding, and hemorrhage from multiple sites. Less often patients present with peripheral thromboses and gangrenous changes in their digits, genitalia and nose. Some patients, especially those with chronic DIC in malignancy, have laboratory abnormalities without any evidence of thrombosis or hemorrhage.

The laboratory manifestations include thrombocytopenia, schistocytes were fragmented blood cells on the peripheral smear, prolonged PT and PTT, and decreased fibrinogen level. Individuals also have elevated fibrin split products. The cardinal manifestation of DIC which correlates most closely with bleeding is the plasma fibrinogen level. Low fibrinogen levels are associated with more bleeding.

Liver disease

Liver disease can result in the decreased synthesis of blood clotting proteins. There are many causes of hemorrhage in patients with liver disease: anatomic factors like portal hypertension, peptic ulceration and gastritis; hepatic function abnormalities like decreased synthesis of procoagulant proteins, and decreased synthesis of coagulation inhibitors, the impaired absorption and metabolism of vitamin K, and the failure to clear activated coagulation proteins.

It is important to recognize that bleeding is usually due to an anatomic lesion but then is exacerbated by the hemostatic defect. Most patients bleed from complications of portal hypertension such as esophageal varices or from gastritis and peptic ulceration of the gastrointestinal tract. Portal hypertension also causes splenomegaly with splenic sequestration of platelets and thrombocytopenia.
Patients with hepatocellular liver disease cannot store vitamin K and may have some degree of vitamin K deficiency. Patients may also have decreased production of other coagulation proteins including fibrinogen and factor V. The liver also produces inhibitors of coagulation such as anti-thrombin three and protein C and S. and is the clearance site for activated coagulation factors and fibrinolytic enzymes. The, patients with liver disease are also hypercoagulable and predisposed to developing DIC or systemic fibrinolysis. For these reasons coagulation defects in advance of her failure are often difficult to distinguish from those of DIC.

Replacing clotting factors

Fresh frozen plasma is the only source of all clotting factors, but it is also a dilute source of any single clotting factor. To replace clotting factors, fresh frozen plasma as indicated before surgical procedures. Factor VII is the most difficult to replace because of the shortness of the plasma half-life. Giving two units of fresh frozen plasma the day before surgery may help incrementally increase clotting factor with longer plasma half lives, but the factor VII provided by those units will be gone by the next day. To increase the factor VII level and decrease the prothrombin time, fresh frozen plasma must be given within 4-6 hours of a procedure.

Cryoprecipitate contains primarily fibrinogen, von Willebrand factor with factor VIII, factor XIII, fibronectin. Cryoprecipitate contains only trace amounts of clotting factors other than those listed. Cryoprecipitate is typically used in patients with low fibrinogen levels, like those with acute DIC.

A few useful tests

**APTT** measures intrinsic pathway of coagulation which includes factors XII, XI, IX, VIII, X, V, II and I; any deficiency, inhibitor or dysfunctional molecule will cause its prolongation.

**APTT MIX** APTT done on patient plasma mixed with normal plasma to determine if an inhibitor is present. Failure of a previously long APTT to correct after mixing indicates inhibition

**FACTOR VIII AND IX** specific functional assays using plasma deficient in these factors and measuring the degree of correction of corresponding APTT

**THROMBIN TIME** measures the conversion of fibrinogen to fibrin after the addition of thrombin; any deficiency, inhibitor or dysfunctional molecule of fibrinogen may prolong it. Also heparin inhibits thrombin and prolongs thrombin time.

**VWF AG** an antigenic test using heterologous rabbit antibody for high molecular weight of portion of factor VIII molecule (Von Willebrand factor). It is low in some types of von willebrand disease and elevated in hemophilia A.
RCOF (RISTOCETIN COFACTOR) is a functional test for the high molecular weight portion of factor VIII molecule (von willebrand factor) that is low in Von Willebrand disease and normal or elevated in hemophilia A.