

Coagulation complications in LIVER FAILURE

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Bleeding complications in patients with advanced liver disease can be very severe and even fatal and directly account for about 20% of the deaths associated with hepatic failure. The extent of the bleeding tendency depends on the severity and type of liver disease involved.

PATHOPHYSIOLOGY.

The pathophysiology of bleeding in liver failure is complex and multifactorial. Anatomic abnormalities are frequently the major cause of gastrointestinal bleeding in patients with liver disease. These changes usually result from portal hypertension.

Upper gastrointestinal bleeding can be caused by esophageal varices or hemorrhagic gastritis (congestive gastropathy), whereas lower gastrointestinal bleeding, although seldom life-threatening, can be due to hemorrhoids.

The liver is the principal organ site for the synthesis of coagulation and fibrinolytic factors and their protein inhibitors **Hepatocytes produce all of the clotting factors except von Willebrand factor**, and advanced parenchymal liver disease therefore results in impaired synthesis of these proteins. When liver synthesis of clotting factors is impaired and results in hepatocellular dysfunction, there is inadequate absorption of vitamin K, which is required for the synthesis of factors II, VII, IX, and X. In addition to a quantitative deficiency of fibrinogen, functional abnormalities of this protein, termed **dysfibrinogenemias**, are frequently found in various forms of liver disease, particularly in hepatomas.

CLOTTING- How it works

Normal hemostasis occurs in two stages:

- **Primary hemostasis**: in which a loose 'plug' is produced at the site of vessel damage to temporarily arrest blood loss. Vasoconstriction restricts the amount of bleeding from the severed vessel. Changes in the endothelium as a result of vessel damage result in the adherence of platelets to collagen in the exposed subendothelial tissues. **Platelet aggregation ensues to form the primary hemostatic plug**.
- **Secondary hemostasis**: once the platelet aggregate is formed, the process of coagulation aids the production of a stable clot. The platelets stimulate the sequential activation of plasma coagulation factors, which result in the **formation of a tough fibrin mesh around the initial hemostatic plug**. Once tissue healing is complete, the clot is gradually broken down by the process of fibrinolysis. Both coagulation and fibrinolysis are modified by plasma inhibitors.

There are 2 paths involved in the Physiology of Clotting. **See Figure-1.**

At the end, both pathways converge, and Factor X may be activated by two different proteases: By factor IX_a (Christmas factor) a product of the intrinsic pathway and factor VII_a (proconvertin) the product of the extrinsic pathway.

1. Intrinsic Pathway

The **intrinsic pathway requires the clotting factors VIII, IX, X, XI, and XII**. Also required are the proteins prekallikrein and high-molecular-weight kininogen, as well as calcium ions and phospholipids secreted from platelets. Each of these pathway constituents leads to the conversion of factor X (inactive) to factor X_a ("a" signifies active). Initiation of the intrinsic pathway occurs when prekallikrein, high-molecular-weight kininogen, factor XI and factor XII are exposed to a negatively charged surface. This is termed the **contact phase**. **Exposure of collagen to a vessel surface is the primary stimulus for the contact phase**.

The assemblage of contact phase components results in conversion of prekallikrein to **kallikrein**, which in turn activates factor XII to **factor XIIa**. Factor XIIa can then hydrolyze more prekallikrein to kallikrein, establishing a reciprocal activation cascade. Factor XIIa also activates factor XI to **factor XIa** and leads to the release of **bradykinin**, a potent vasodilator, from high-molecular-weight kininogen. In the presence of Ca²⁺, factor XIa activates factor IX to **factor IXa**. Factor IX is a proenzyme that contains **vitamin K-dependent g-carboxyglutamate (gla)** residues, whose serine protease activity is activated

following Ca^{2+} binding to these gla residues. Several of the serine proteases of the cascade (II, VII, IX, and X) are gla-containing proenzymes. Active factor IXa cleaves factor X at an internal arg-ile bond leading to its activation to **factor Xa**.

The activation of factor Xa requires assemblage of the **tenase complex** (Ca^{2+} and factors VIIIa, IXa and X) on the surface of activated platelets. One of the responses of platelets to activation is the presentation of phosphatidylserine and phosphatidylinositol on their surfaces. The **exposure of these phospholipids allows the tenase complex to form**. The role of factor VIII in this process is to act as a receptor, in the form of factor VIIIa, for factors IXa and X. Factor VIIIa is termed a **cofactor** in the clotting cascade. The activation of factor VIII to **factor VIIIa** (the actual receptor) occurs in the presence of minute quantities of thrombin. As the concentration of thrombin increases, factor VIIIa is ultimately cleaved by thrombin and inactivated. This dual action of thrombin, upon factor VIII, acts to limit the extent of tenase complex formation and thus the extent of the coagulation cascade.

2. Extrinsic Pathway

Activated factor Xa is the site at which the intrinsic and extrinsic coagulation cascades converge. The **extrinsic pathway is initiated at the site of injury in response to the release of tissue factor (factor III)**. Tissue factor is a **cofactor** in the factor VIIa-catalyzed activation of factor X. Factor VIIa, a gla residue containing serine protease, cleaves factor X to factor Xa in a manner identical to that of factor IXa of the intrinsic pathway. The activation of factor VII occurs through the action of thrombin or factor Xa.

The ability of factor Xa to activate factor VII creates a link between the intrinsic and extrinsic pathways. An additional link between the two pathways exists through the ability of tissue factor and factor VIIa to activate factor IX. The formation of complex between factor VIIa and tissue factor is believed to be a principal step in the overall clotting cascade. Evidence for this stems from the fact that persons with hereditary deficiencies in the components of the **contact phase** of the intrinsic pathway do not exhibit clotting problems.

3. Combining the Paths

Activation of Prothrombin to Thrombin

The **common point in both pathways is the activation of factor X to factor Xa**. Factor Xa activates **prothrombin** (factor II) to **thrombin** (factor IIa). Thrombin, in turn, converts fibrinogen to fibrin. The activation of thrombin occurs on the surface of activated platelets and requires formation of a **prothrombinase complex**. This complex is composed of the platelet phospholipids, phosphatidylinositol and phosphatidylserine, Ca^{2+} , factors Va and Xa, and prothrombin. Factor V is a **cofactor** in the formation of the prothrombinase complex, similar to the role of factor VIII in **tenase complex** formation. Like factor VIII activation, factor V is activated to factor Va by means of minute amounts and is inactivated by increased levels of thrombin. Factor Va binds to specific receptors on the surfaces of activated platelets and forms a complex with prothrombin and factor Xa.

Within the prothrombinase complex, prothrombin is cleaved at 2 sites by factor Xa. In addition to its role in activation of fibrin clot formation, thrombin plays an important regulatory role in coagulation. Thrombin combines with **thrombomodulin** present on endothelial cell surfaces forming a complex that converts protein C to **protein Ca**. The cofactor **protein S** and protein Ca degrade factors Va and VIIIa, thereby limiting the activity of these 2 factors in the coagulation cascade.

INTRINSIC PATHWAY

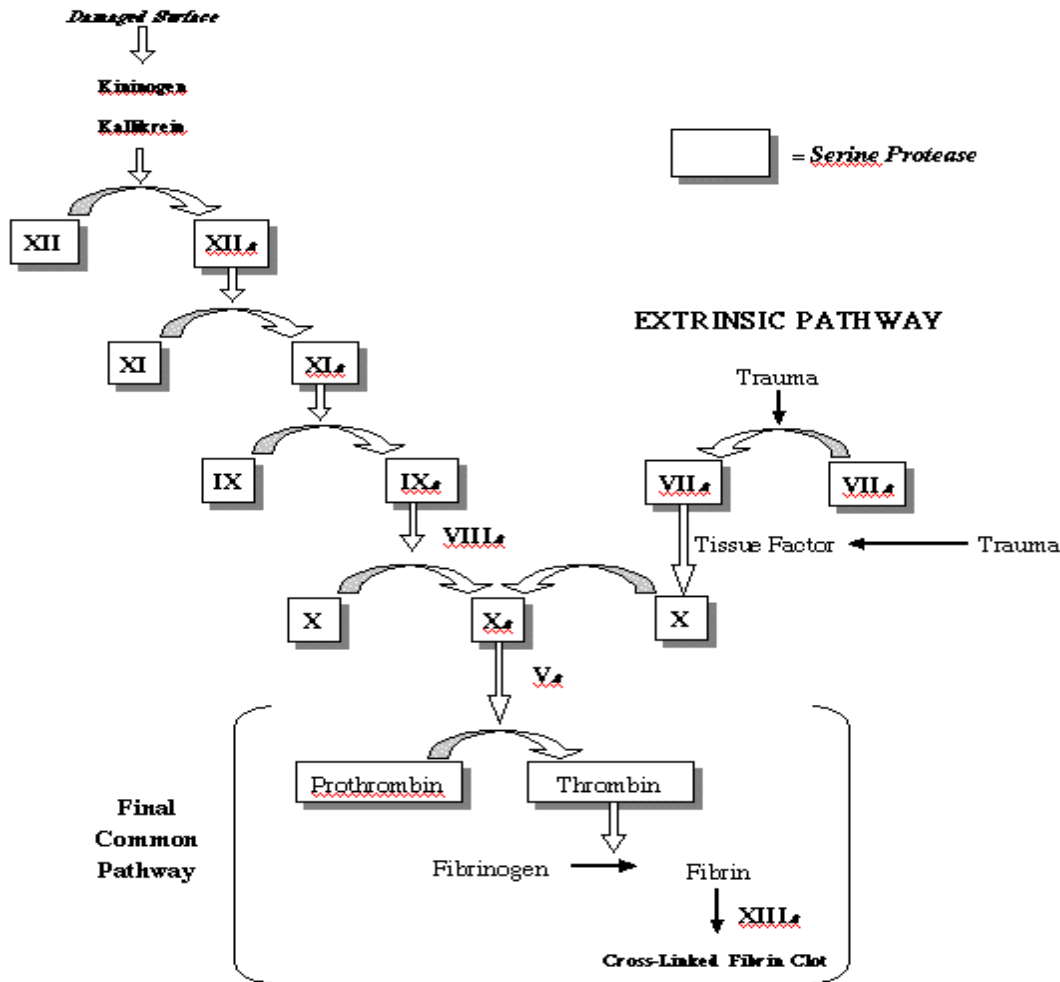


Figure-1. The clotting

cascades. The intrinsic cascade is initiated when contact is made between blood and exposed endothelial cell surfaces. The extrinsic pathway is initiation upon vascular injury which leads to exposure of tissue factor (TF) (also identified as factor III), a subendothelial cell-surface glycoprotein that binds phospholipid.

Control of Thrombin Levels and Clotting

The inability of the body to control the circulating level of active thrombin would lead to dire consequences.. At each step in the cascade, feedback mechanisms regulate the balance between active and inactive enzymes.

The activation of **thrombin is also regulated** by 4 specific thrombin inhibitors. **Antithrombin III = most important** since it can also inhibit the activities of factors IXa, Xa, XIa and XIIa. The **activity of antithrombin III is potentiated in the presence of heparin** by the following means: heparin binds to a specific site on antithrombin III, producing an altered conformation of the protein, and the new conformation has a higher affinity for thrombin as well as its other substrates. **This effect of heparin is the basis for its clinical use as an anticoagulant.** The naturally occurring heparin activator of antithrombin III is present as heparan and heparan sulfate on the surface of vessel endothelial cells. It is this feature that controls the activation of the intrinsic coagulation cascade.

Of note, **α_1 -antitrypsin is the primary serine protease inhibitor** of human plasma. Its physiological significance is demonstrated by the fact that lack of this protein plays a causative role in the development of **emphysema**.

Most forms of advanced liver disease are accompanied by some degree of DIC caused by impaired synthesis of inhibitors of blood coagulation and defective hepatocellular clearance of activated coagulation factors.

Congestive splenomegaly secondary to portal hypertension causes increased pooling of platelets in the spleen (hypersplenism). The resultant **thrombocytopenia**, the degree of which generally correlates with spleen size, rarely causes a reduction in the platelet count below **50,000/mm³**. In alcoholic patients, suppression of bone marrow thrombopoiesis by the acute toxic effects of alcohol or folate

deficiency may contribute to the thrombocytopenia. Qualitative platelet abnormalities have also been described in patients with liver disease.

CLINICAL MANIFESTATIONS.

The most common hemorrhagic complication of acute liver disease is gastrointestinal bleeding, which is usually caused by anatomic abnormalities and exacerbated by the systemic coagulopathy of liver failure. IN these patients, the **transfusion requirements** for coagulation products (fresh frozen plasma, platelets) **may be enormous.** Multiple transfusions with packed red blood cells may be needed. Gastrointestinal bleeding may develop from esophageal, gastric, or ectopic varices as a result of portal hypertension. Portal hypertensive gastropathy and stress gastritis also may develop. Any minor trauma may result in extensive percutaneous bleeding or internal hemorrhage.

DIAGNOSIS and TESTS.

We know that the **clotting factors** that are produced by the liver are I, II, V, VII, IX and X. Also, **coagulation factors** produced in the liver include factors I (fibrinogen), II (thrombin), V, VII, IX and X.

The **order** in which the levels of these factors are reduced in **liver disease** can be found in **Table-1.**

Progression of factors moves top to bottom:

<u>clotting factors</u>	<u>coagulation factors</u>
VII	factor VII
II, X	factors II and X
I, V - these persist despite severe liver disease	

Routine **coagulation tests** are usually sufficient to diagnose the coagulopathy of liver failure. See **Table -3.** Although both the PT and aPTT are often prolonged in advanced liver disease, the former tends to be a more sensitive assay early in the course; in fact, **a disproportionate prolongation of the aPTT should raise suspicion of a coexisting coagulation abnormality, such as a lupus anticoagulant or clotting factor inhibitor.**

TABLE-2 -- COAGULATION ABNORMALITIES IN LIVER DISEASE

<i>Abnormalities of Coagulation</i>
Decreased synthesis of coagulation factors
Impaired vitamin K-dependent gamma-carboxylation
Dysfibrinogenemia
Disseminated intravascular coagulation
Increased fibrinolytic activity
<i>Abnormalities of platelets</i>
Thrombocytopenia (hypersplenism)
Abnormal platelet function

Table-3

Test	Discription
One-Stage Prothrombin Time (PT)	<ul style="list-style-type: none"> Mixture consisting of plasma, tissue thromboplastin (III) and calcium measure of the efficiency of the extrinsic blood coagulation pathway. Normal values of 11 to 14 seconds are found depending on the tissue thromboplastin (III) used. A prolonged clotting time may result form a deficiency of one or more of the following; Proaccelerin (V), Proconvertin (VII), Stuart factor (X), prothrombin (II) or fibrinogen (I). This test is most commonly used to monitor anticoagulant therapy with coumadin drugs and as a test of liver function.
Partial-Thromboplastin Time (PTT)	<ul style="list-style-type: none"> PTT is a test of all stages of the intrinsic clotting pathway except platelet factor 3. Normal values usually lie between 60 and 90 seconds.

Thrombin Time	<ul style="list-style-type: none"> • In the normal range results are usually reproducible within a 2-second range. • A prolonged thrombin clotting time results from a deficiency of fibrinogen, • If the patient's thrombin time is more than 1.3 times longer than that of the control, the difference is probably significant. • The inhibitor most likely to prolong the thrombin time are heparin and fragments of fibrinogen that result from fibrinolysis.
Platelet count	<ul style="list-style-type: none"> • Platelets are the smallest of the blood cells • In some individuals with liver disease, the spleen becomes enlarged as blood flow through the liver is impeded. • This can lead to platelets being sequestered in the enlarged spleen. • In chronic liver diseases, the platelet count usually falls only after cirrhosis has developed. The platelet count can be abnormal in many conditions other than liver diseases.

The **prolonged PT is also a useful prognostic indicator** of poor outcome in patients with cirrhosis, acute acetaminophen hepatotoxicity, and acute viral hepatitis; in the latter, it is a better index of prognosis than the serum albumin or transaminases. A disproportionate prolongation of the thrombin time should suggest the presence of dysfibrinogenemia.

The **coagulopathy of liver failure is sometimes indistinguishable from that of DIC**, in part because some degree of DIC is a necessary accompaniment of advanced liver disease. However, in general, patients with DIC have more marked decreases in levels of Factor VIII and increases in titers of FDPs, particularly D-dimers, than do those with liver failure.

How do we TREATMENT?

Therapy for the coagulopathy of liver disease may be directed at preventing the hemorrhagic complications of invasive procedures or treating active bleeding. Bleeding risks of surgical procedures in patients with liver failure are poorly defined. However, it is usually recommended that attempts be made to **correct PT prolongations of over 3 seconds and platelet counts below 70,000/mm³ before surgical interventions**, including percutaneous liver biopsy. The **most effective treatment is blood component therapy with fresh-frozen plasma** (which contains all of the coagulation factors) and platelet transfusions. Some patients require large volumes of fresh-frozen plasma (15 to 20 mL/kg) to lower the prolonged PT; rarely, plasmapheresis with plasma exchange is required to avoid fluid overload in such situations. Because of the short half-lives of some clotting factors, fresh-frozen plasma may have to be administered as frequently as every 8 to 12 hours to maintain acceptable coagulation test parameters. In some patients, especially those with cholestasis, parenteral administration of vitamin K can at least partially reverse the coagulation abnormalities; however, in patients with advanced hepatocellular failure, vitamin K is largely ineffective. Prothrombin complex concentrates are relatively contraindicated in liver failure, as in DIC, because of the risk of thrombotic complications.

===== **The Transjugular Intrahepatic Portal-Systemic Shunt (TIPS) Procedure**

The transjugular intrahepatic portal-systemic shunt, or TIPS, procedure is not a surgical operation -- **a radiologist performs the procedure in the x-ray room under x-ray guidance.**

During the TIPS procedure, a radiologist places a stent (a tubular device) in the middle of the liver to reroute blood flow from the portal vein, which leads to the liver, directly into the hepatic veins and to the vena cava (the largest vein leading from the liver to the heart). **The TIPS procedure reroutes blood flow around the liver and reduces pressure in all abnormal veins** -- not only in the stomach and esophagus, but also in the bowel and liver. **TIPS provides immediate control of variceal bleeding in more than 90 percent of patients.**

The procedure lasts from 1 to 3 hours. Patients usually remain in the hospital for two to three days after the procedure. Before discharge, the physician orders a repeat Doppler sonogram to determine whether the shunt is functioning properly. At the time of discharge, a **patient is taking lactulose** (for constipation and disturbances of the nervous system) and some type of antacid medication. Patients must continue to take these medications until their physician advises them to stop. Also, before discharge, a patient receives a list of dietary recommendations to ensure that he or she maintains a low-salt, low-protein diet.