Thrombohaemorrhagic coagulopathies: Disseminated Intravascular Coagulation

DIC is a syndrome of increased propensity for clot formation triggered by a pathological stimuli that disrupts the coagulation balance (e.g. massive release of tissue factor or direct activation of coagulation factors) resulting in a fibrin clot that disseminates or spreads throughout the microcirculation. Hence the term "Disseminated Intravascular Coagulation".

The activation of coagulation along with accompanying fibrinolysis causes uncontrolled consumption of coagulation factors and platelets, generation of thrombin as well as plasmin and formation of Fibrin Degradation products. This hematologic manifestation is also referred to as Consumptive Coagulopathy and is associated with variable pathological disorders. In DIC, the fibrin thrombi so formed may be microscopic and clinically inconspicuous, hence early recognition and diagnosis of DIC is solely dependent on effective laboratory testing.

To understand the complexity in DIC, let us first briefly review the Hemostatic mechanism.

Haemostasis:

Haemostasis is a complex interaction to prevent the loss of blood at the site of injury and to maintain the fluid state of blood after the wound is healed.

Haemostasis is a delicate balance between clot formation and clot dissolution. It involves the interaction of vascular endothelium, platelets, coagulation factors and fibrinolytic proteins.

Coagulation:

In a non -pathologic state, the normal response to intravascular trauma or tissue injury is a stable fibrin clot, required to prevent the excess loss of blood. During intravascular injury, platelets adhere to the damaged endothelial cells via the exposed collagen and aggregate to form a Primary Platelet Plug. The Intrinsic Pathway is activated when factor XII binds to the Primary Platelet Plug.

During tissue injury, Tissue Factor (factor III) is released from the damaged organ which activates factor VII thereby initiating clot formation via the Extrinsic Pathway.

The Intrinsic and Extrinsic Pathways proceed through a series of enzymatic reactions, which results in the formation of Thrombin from Prothrombin. Thereafter the Pathways proceed via the Common Pathway resulting in the formation of a stable Fibrin Clot.

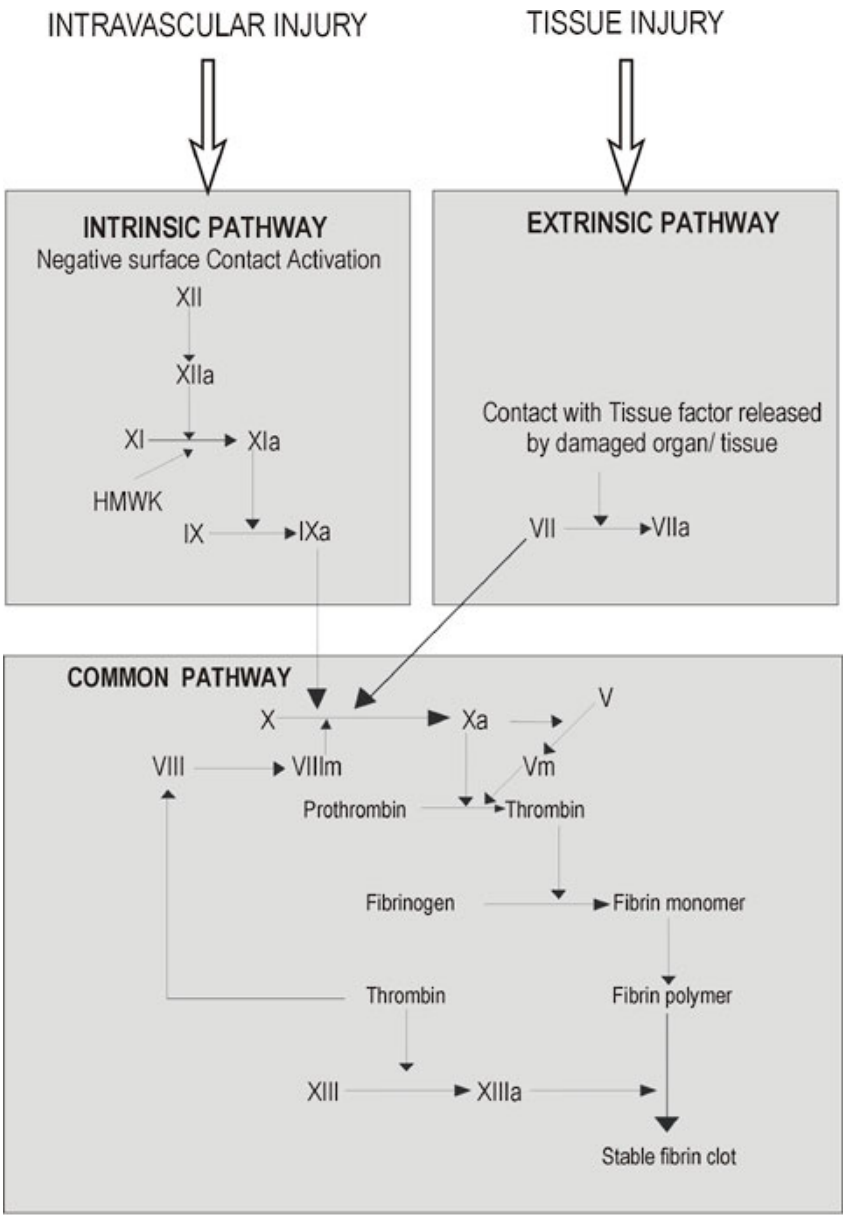

Figure 1: Coagulation pathways

Fibrinolysis:

After the formation of a stable fibrin clot, the healing process starts. Once the wound is healed, the clot is dissolved so as to restore the flow of blood through the healed vessel. The process of clot dissolution is known as Fibrinolysis and is brought about by a protein Plasmin.

Plasmin is present in its inactive form Plasminogen. Plasminogen is activated to Plasmin either by Kallikrein generated by the Intrinsic pathway, Tissue Plasminogen Activator from injured endothelial cells or Urokinase produced by kidney endothelial cells.

Through a series of enzymatic reactions much like coagulation, Plasmin degrades the fibrin clot into Fibrin Degradation Products (FDP). The FDP's include fragments X and Y (early splits) and D and E (late splits). D-Dimer or XL-FDP (Cross-linked Fibrin Degradation Product) is the smallest cross-linked fibrin degradation product formed as a result of plasmin activity on the fibrin clot. Thus detection of D-Dimer is specific for an ongoing in vivo thrombotic condition.

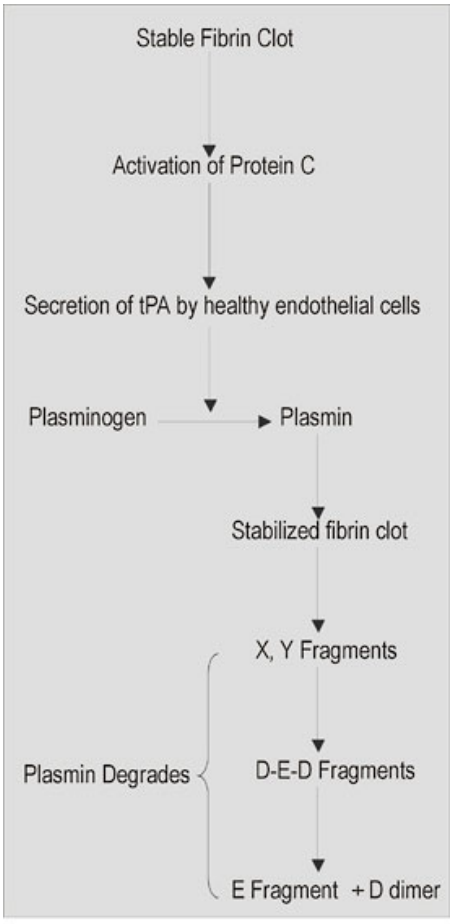

Figure 2: Fibrinolytic System

Primary Fibrinogenolysis:

Primary Fibrinogenolysis or inappropriate fibrinolysis occurs in the absence of an underlying thrombotic tendency (fibrin clot formation). During certain clinical conditions, abnormal high concentration of plasmin in the circulation results in degradation of Fibrinogen into Fibrinogen Degradation Products as well as degradation of activated factor V and factor VIII.

Clinical Conditions	Mode of action
Urological Disease	Release of Urokinase which activates Plasminogen
Renal Disease	Decreased renal clearance of Plasminogen activators; tPA and urokinase
Decreased physiological activity of Plasmin inhibitors (α 2 antiplasmin and α 2 macroglobulin)	Results in uncontrolled plasmin action on Fibrinogen and activated factors V and VIII

Hence in Primary Fibrinogenolysis, due to absence of a stable fibrin clot the D-Dimer level in the circulation would be within the Normal range. D-Dimer or XL-FDP test serves a efficient tool in differential diagnosis of DIC and Primary Fibrinogenolysis.

Etiology of Disseminated Intravascular Coagulation:

DIC occurs when pathological stimuli disrupts the haemostatic balance which may be due to damage or alteration of any of the major components of haemostasis which facilitates fibrin clot formation. The factors that cause DIC syndrome are multiple and associated with well-defined clinical conditions.

The most common causative stimulus of DIC are mentioned below along with their probable pathogenesis:

Common Causes of DIC and Probable pathogenesis:

Stimulus	Probable pathogenesis
Septicaemia by gram negative bacteria	Endotoxin induce: ➢ Release of thromboplastin from monocytes ➢ Endothelial cells damage and activation of factor XII
Malignancies Acute promyelocytic leukemia, acute myelomonocytic leukemia, Solid tumors	Release of thromboplastin from cancer cells and granules of monocytes
Intravascular haemolysis Transfusion reaction, Sickle cell anemia	Release of RBC membrane phospholipid and interaction with endothelial cells
Vascular malformation **Giant hemangioma**	➢ Large gaps in endothelium ➢ Exposed subendothelial collagen and release of thromboplastin from poorly supported recurrent injured vessels in tumor**.**
Snake envenomation	➢ Venom specifically activate factor X or Prothrombin ➢ Some venoms also contain thromboplastin which produce Intravascular haemolysis
Burns, traumatic injuries	Release of thromboplastin from damaged tissues
Collagen vascular disease	Probable platelet aggregation and factor XII activation by antigen-antibody complex

Pathophysiology of DIC:

Activation of the coagulation system leads to formation of thrombin and plasmin. Thrombin, on one hand facilitates the formation of a stable fibrin clot. This disseminated fibrin clot travels to microcirculation/ capillaries or smaller vessels, obstructing the flow of blood to the tissue. Lack of blood supply due to obstruction results in decreased tissue oxygenation, organ infarction and necrosis. The release of tissue factor from the organ contributes to continued uncontrolled intravascular fibrin formation as well as plasmin activation.

Plasmin on the other hand, degrades the cross-linked fibrin clot, demonstrated by the presence of Fibrin Degradation Products, as well as D-Dimer in the circulation.

This combination of uncontrolled coagulation and fibrinolysis leads to consumption of coagulation factors and platelets. As the rate of clot formation exceeds the rate of synthesis of coagulation factors and platelets, a bleeding tendency develops along with shock and vascular occlusion. In addition, the patient's liver is overworked by the need to produce more coagulation factors as well as remove the FDPs.

Diagrammatic representation of Pathophysiology of DIC:

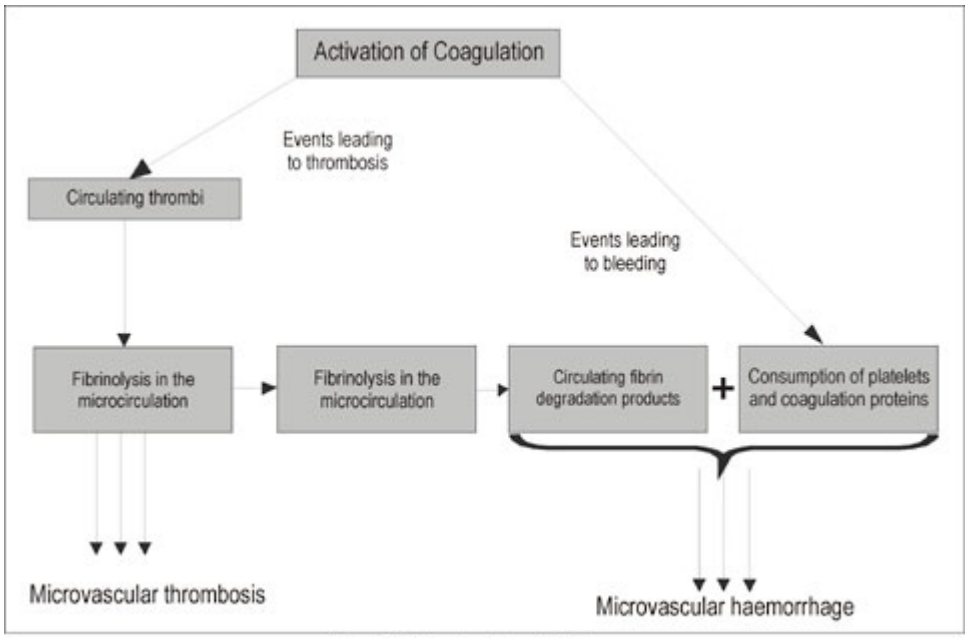

Figure 3: Pathophysiology of DIC

Clinical Symptoms:

The clinical symptoms and laboratory presentation of the syndrome is affected by various parameters and is also influenced by the underlying disease conditions that cause this syndrome.

The classical clinical symptoms of DIC depends upon the patient's:

- Functional ability of the liver to produce coagulation factors and remove FDPs
- Bone marrow ability to replace platelets consumed

Clinical symptoms and presentation of DIC can be divided into 2 broad spectrums; Acute Uncompensated DIC and Chronic Compensated DIC.

Acute Uncompensated DIC:

Acute Uncompensated DIC occurs with the advent of a precipitating event or underlying disease condition. The initial pathological event leads to a thrombotic tendency but later acute DIC syndrome presents itself with haemorrhagic symptoms associated with ecchymoses, epistases, bleeding from needle puncture sites. The symptoms may develop after a few hours to a few days after the stimulus activates uncontrolled clot formation.

The occurrence of a haemorrhagic condition arises in acute DIC, as the patient's liver and bone marrow cannot produce coagulation factors and platelets fast enough to compensate for their increase uncontrolled consumption. Hence this condition is known as Acute Uncompensated DIC. Patients with acute uncompensated DIC have the highest mortality risk due to the haemorrhagic state

Acute DIC is relatively easy to diagnose as the patient presents with a bleeding tendency.

Chronic Compensated DIC:

In contrast to Acute DIC, Chronic Compensated DIC presents with mild, less obvious clinical symptoms.

Chronic DIC occurs when the clot formation and accompanying fibrinolysis are in a slow steady state and thus the liver and bone marrow can compensate for the consumption of factors and platelets while still clearing the FDPs.

Hence in this condition, bleeding tendency is much less evident and therefore a reliable diagnosis must be available to allow appropriate therapy, which can be made only on the basis of laboratory tests.

Chronic DIC if not diagnosed and successfully treated, or the underlying disease still persists, can lead to Acute DIC and ultimately patient death.

Clinical Conditions associated with Acute Uncompensated DIC and Chronic Compensated DIC:

Acute Uncompensated DIC	Chronic Compensated DIC
Obstetrical Complications	Obstetrical Complications
Septicemia (Gram Negative Bacteria)	Metastatic Malignancy
Traumatic Injuries	Collagen / Vascular disease
Burns	RBC Related hematologic disease (Polycythemia Vera)
Acute Promyelocytic Leukemia	-
Poisonous Snake Bite	-
Liver disease	-

Diagnosis of DIC:

No test is specific for DIC, however laboratorians provide physicians with a panel of tests that include PT, APTT, Fibrinogen, Platelet count, Fibrin (ogen) Degradation Product test and D-Dimer (XL FDP) tests .

Presented below is a list of tests and their outcomes in Acute and Chronic DIC:

Test	Acute Uncompensated DIC	Chronic compensated DIC
PT	Prolonged	Normal/ Prolonged
APTT	Prolonged	Normal/ Prolonged
Fibrinogen	Decreased	Normal/ Elevated
Platelet count	Decreased	Normal/ Decreased

From the above table it is evident that these test can indeed indicate changes in the Haemostasis mechanism for Acute DIC where as in Chronic DIC, such changes are not evident. The PT, APTT,

Fibrinogen and Platelet count results may be normal in Chronic Compensated DIC as the patient's liver can cope with the uncontrolled consumption of factors. The PT and APTT tests also suffer form the drawback that these tests are affected by the presence of oral anticoagulants, heparin or circulating Inhibitors e.g. LA.

Test	Acute Uncompensated DIC	Chronic compensated DIC
FDP test	Increased	Increased
D-Dimer	Increased	Increased

It is observed that Fibrin (ogen) Degradation Products are elevated in patients with DIC therefore a FDP test is recommended as it is extremely sensitive and measures fibrinolysis (plasmin biodegradation of fibrin) and or Fibrinogenolysis (plasmin biodegradation of fibrinogen) with no false negatives. A positive outcome of an FDP test should indicate DIC. However FDP test is not specific for DIC as elevated levels of FDP's are present after intense exercise/ workout, in patients with decreased renal clearance due to the presence of Plasmin activators and during pregnancy.

D-Dimer test or XL FDP test is a better indicator for DIC as the D-Dimer test is specific for the cross-linkage in the endpoint D-D fragments produced as a result of active plasmin activity on the stable fibrin clot. In addition to the fibrinolytic activity of Plasmin, the presence of D-Dimer indicates the coagulant activity of thrombin and hence a D-Dimer test has the best positive predictive value for DIC.

In normal healthy individuals, due to constant wear and tear, clots are constantly formed and dissolved. It has been observed that, in normal individuals with appropriate renal clearance, D-Dimer level is less than 200ng/ml. Therefore the cut-off of a D-Dimer test should be adjusted to 200ng/ml. Hence commercially available kits have a cut-off adjusted at ³ 200ng/ml of D-Dimer in plasma.

Two types of FDP tests are currently available;

- Serum FDP test
- Plasma FDP test

A serum FDP test utilizes polyclonal antibodies directed against either Fibrinogen or Fibrin degradation Product. The assay utilizes serum as the sample so as to remove the inference of fibrinogen and its degradation products. However, this results in entrapment of the cross-linked D-Dimer in the clot leading to false negative results. This assays also detects artificially generated fragments due to serum generation.

With the advent of the monoclonal technology, antibodies specific for the cross linkage have being developed. The test assay is simple and convenient, as no special collection procedures are required, no loss of the cross linked FDP through the entrapment of the clot. The assay is also free from interference of Fibrinogen and its degradation products and is insensitive to the presence of heparin. Thus plasma FDP test is the test of choice for diagnosis of DIC.

To conclude, DIC is a thrombohemorragic syndrome that occurs when a clinical stimuli disrupts the delicate Haemostatic balance leading to uncontrolled thrombosis accompanied with haemorrhagic condition. Early diagnosis of the condition with the aid of a Plasma FDP test can translate into the successful therapy and better patient management.

References:

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