INTRODUCTION

The coagulation system in the body consists of clotting and fibrinolytic mechanisms. The function of the former is to prevent excessive blood loss, whereas the latter is to ensure circulation within the vasculature. Following an insult, the activated coagulation cascade adequately balances the naturally occurring anti-coagulant systems and the fibrinolytic system (which generates plasmin) to maintain a normal circulation. In disseminated intravascular coagulopathy (DIC) like syndrome, there is widespread activation of the blood coagulation system leading to excessive generation and disseminated deposition of fibrin clots in small and midsize vessels, which alters the microcirculation leading to ischaemic necrosis in various organs particularly in kidney and lung resulting in organ failure. There can be concomitant consumption of platelets and coagulation factors resulting in serious haemorrhagic complications which sometimes may be the most striking clinical presentation. Hence, a patient with DIC can present as thrombotic and bleeding problem simultaneously [Figure 1].

Disseminated intravascular coagulopathy should not be considered as a distinct disease entity but rather a sign of another disease. It has been associated with almost all life-threatening diseases. The clinical spectrum of DIC can range from a small decrease in platelet count and sub-clinical prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT) to a fulminant DIC with widespread thrombosis and severe bleeding. Any tissue insult sufficient enough to release tissue products or toxins into the circulation can result in DIC. This review will focus on definition, aetio-pathogenesis, diagnosis and management of DIC.

DEFINITION

A widely accepted definition put forward by the subcommittee on DIC of the Scientific and...
Standardisation Committee of the International Society on Thrombosis and Haemostasis (ISTH) is as follows: DIC is an acquired syndrome characterised by the intravascular activation of coagulation with loss of localisation arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.[3]

**AETIO-PATHOGENESIS OF DISSEMINATED INTRAVASCULAR COAGULOPATHY**

DIC occurs secondary to a clinical disorder which provides a key for appropriate investigation and management. The clinical spectrum includes sepsis, trauma, malignancy, liver disease, obstetric disorders, envenomation, vascular anomalies and major transfusion reactions [Table 1]. The pathogenesis may follow either or both of the following pathways:

a. As a part of systemic inflammatory response, there is activation of cytokine network and thereby coagulation system as in sepsis or polytrauma and/or

b. Release of pro-coagulant material to the blood stream as in malignancies or obstetrical cases.

Bacterial septicaemia accounts for the major cause of DIC which may be due to either cell membrane components of the microorganism or bacterial exotoxins.[3] In severe trauma, release of phospholipids and fat (major fractures) into the circulation can cause haemolysis, endothelial damage and activation of the coagulation cascade.[4] Solid tumours and haematological malignancies particularly acute pro-myelocytic leukaemia and some forms of prostatic cancer are associated with DIC.[5] Tumour cells can produce various pro-coagulant molecules including tissue factor and a cancer pro-coagulant, which is a cysteine protease with factor X activating properties.[6] Compared to sepsis and trauma, DIC in cancer is found to have a less fulminant presentation. A more chronic and gradual systemic activation of coagulation leads to sub-clinical progression and finally bleeding at the site of the tumour. Acute obstetric complications such as abruptio placenta, amniotic fluid embolism, rarely pre-eclampsia and intruterine death of the foetus can also lead to DIC. Release of thromboplastin-like material in abruptio placenta is the causative factor which correlates with the degree of separation. Aortic aneurysms and cavernous haemangiomas may promote DIC by producing vascular stasis or local activation of coagulation system; whereas snake
bites cause exogenous toxins induced DIC. Though microangiopathic haemolytic anaemia can mimic DIC clinically, it can be differentiated from it by normal PT and aPTT which are usually prolonged in DIC.

Several mechanisms occurring simultaneously play an effective role in the development of DIC. Excess thrombin generation, as a result of bacteraemia or endotoxaemia, is insufficiently balanced by impaired anti-coagulant systems such as anti-thrombin and protein C. This results in excess fibrin generation and deposition in the vascular system. In the early phase of DIC, plasmin (naturally occurring fibrinolytic agent) produced by the activation of plasminogen activators from the endothelial cells causes fibrinolysis to maintain circulation. But, its effect is immediately offset by high circulating levels of plasminogen activator inhibitor-1, a fibrinolytic inhibitor. Bleeding manifestation, seen in some forms of DIC, is due to the excess fibrinolytic activity.

There are three major natural anti-coagulants in the vascular system. They are anti-thrombin III, protein C and the tissue factor pathway inhibitor (TFPI). Studies have shown that thrombin generation in DIC is tissue factor driven (tissue factor/factor VIIa) with intrinsic pathway playing a minor role. Anti-thrombin III is the most important inhibitor of thrombin in the coagulation cascade. Markedly reduced concentration of this factor in sepsis has been implicated in the pathogenesis of DIC and organ dysfunction. Impairment of protein C pathway is mainly caused by down-regulation of thrombomodulin expression on endothelial cells by pro-inflammatory cytokines like tumour necrosis factor-alpha and interleukin-1 beta. This has been confirmed in meningococcal sepsis also. Pro-inflammatory cytokines along with low levels of zymogen protein C leads to reduced protein C activation resulting in a pro-coagulant state. TFPI is the third significant inhibitor of coagulation and studies have shown that pharmacological doses of TFPI can reduce the mortality associated with systemic infection and inflammation.

**DIAGNOSIS OF DISSEMINATED INTRAVASCULAR COAGULOPATHY**

A diagnosis of DIC should be made only in the presence of a clinical condition (causative factor) supported by relevant laboratory results. A combination of tests when repeated in a patient with a clinical condition known to be associated with DIC can be used for the diagnosis with a reasonable certainty. Degree of coagulation factor consumption and activation can be screened by tests such as PT and aPTT or platelet count. A measurement of D-dimer levels in blood can be assayed which provides an indirect measure of fibrin formation. The laboratory abnormalities reported in DIC listed in the decreasing order of frequency are thrombocytopenia, elevated fibrin degradation products (FDPs), prolonged PT, aPTT and a low fibrinogen. In early DIC, the platelet count and fibrinogen levels may remain within the normal range, albeit reduced from baseline levels.

**THROMBOCYTOPENIA**

Low platelets or a rapidly progressing thrombocytopenia is a key finding in DIC. Moderate (<1 lakh/mm<sup>3</sup>) to severe thrombocytopenia (<50,000/mm<sup>3</sup>) is seen in majority of patients and those with <50,000 have a 4-5 fold increased haemorrhagic complications compared to those with normal count. It is a sensitive but not a specific sign of DIC. Thrombocytopenia is seen in about 98% of cases, with <50,000/mm<sup>3</sup> in about half the cases. It correlates well with thrombin generation as thrombin-induced platelet aggregation is mainly responsible for its consumption. A declining trend rather than a single value is most indicative of DIC. At the same time, it should be remembered that a declining trend is not very specific for DIC because conditions associated with DIC such as acute leukaemia and sepsis can also have thrombocytopenia in the absence of DIC. At the same time, a stable platelet count is an indirect measure to suggest that thrombin formation has stopped.

**FIBRIN DEGRADATION PRODUCTS AND D-DIMERS**

Fibrin degradation product is a measure of increased fibrinolytic activity which is also increased in DIC. New assays have developed which specifically detects the neo-antigens on degraded cross-linked fibrin called the D-dimer. Its level is also found to the elevated in conditions like trauma, recent surgery or venous thromboembolism and hence not a specific test for DIC. It can also be raised in liver and renal impairment as a result of its impaired metabolism and excretion. Hence, it is of value when associated with a declining platelet count and prolonged PT and aPTT. Though much debate is underway regarding the cut-off level of D-dimer, clinician’s experience, available circumstance and other supportive laboratory values are crucial to the diagnosis of DIC. Soluble fibrin monomer offers a
theoretical advantage over FDP in the diagnosis of DIC as it is produced only intravascularly and not found rose in local inflammation and trauma. Though it has a high sensitivity (90-100%), the specificity is very low. However, its incorporation into the ISTH scoring system instead of D-dimer, can improve the specificity of diagnosing DIC.

**PROTHROMBIN TIME AND ACTIVATED PARTIAL THROMBOPLASTIN TIME**

Both PT and aPTT seem prolonged in about 50% of DIC cases which is attributed to the consumption of coagulation factors but can also be prolonged in impaired synthesis of coagulation factors and in massive bleeding.\[19\] At the same time, at least in half the patients with DIC, PT and aPTT are found normal or shortened due to the presence of circulating activated clotting factors like thrombin or Xa. Thus, a normal PT or aPTT do not exclude DIC and repeated monitoring is required.

**FIBRINOGEN**

Fibrinogen is an acute phase reactant and its plasma level can remain elevated for prolonged periods despite ongoing consumption in DIC. Hence, hypofibrinogenaemia for diagnosis of DIC carries very low sensitivity and was associated only with severe forms of DIC.\[14\] Fibrinogen level can be normal in nearly half the patients, and hence, serial measurements are indicated.

More recently, an atypical light transmittance profile on the aPTT has been found to be associated with DIC. This biphasic waveform abnormality occurs independently of prolonged clotting times and studies show it to be a simple, rapid and robust indicator of DIC.\[20,21\] It also carries a high positive predictive value for DIC with increasing waveform abnormality.\[20\]

**SCORING SYSTEM**

The ISTH subcommittee has recommended a scoring system for overt DIC.\[2\] It is a five step diagnostic algorithm to calculate a DIC score based on simple laboratory results [Table 2]. For a diagnosis of overt DIC, a score of 5 or more from four parameters are required and was found to be sensitive to both infective and non-infective causes of DIC.\[21\] The score has a sensitivity of 91% and specificity of 97% and there exists a strong correlation between increasing DIC score and mortality. For each DIC point, increases in the odds of mortality of 1.25-1.29 have been demonstrated.\[22\] Several other studies have also confirmed the scoring algorithm as independent predictor of mortality.\[21,24\] They also showed that patients with sepsis and DIC have a higher mortality of 43% as compared with 27% in patients without DIC. Moreover, this scoring system has added prognostic value in better predicting mortality than the Acute Physiology and Chronic Health Evaluation (APACHE) II score as evidenced by an increase in odds ratio in the ISTH scoring.\[25\]

**DIFFERENTIAL DIAGNOSIS OF DISSEMINATED INTRAVASCULAR COAGULOPATHY**

Differential diagnosis of DIC includes:
1. Massive blood loss
2. Thrombotic microangiopathy
3. Heparin-induced thrombocytopenia
4. Vitamin K deficiency
5. Liver insufficiency.

Additional diagnostic clues are helpful in differentiating it from DIC [Table 3].

**TREATMENT**

Key factor in DIC management is the proper treatment of the underlying cause and that may itself revert or prevent the development of DIC. But sometimes additional supportive treatment aimed at correction of coagulation abnormalities may be required. Blood component therapy should never be instituted on
Venugopal: Disseminated intravascular coagulation

Prolonged aPTT, PT, Platelet count, increased

Major bleeding, low haemoglobin, prolonged aPTT, PT and platelet count.

Schistocytes in blood smear, Coombs-negative haemolysis, fever, neurologic symptoms, renal insufficiency, coagulation times usually normal; ADAMTS13 levels decreased; PT and a PTT normal

Use of heparin, venous or arterial thrombosis, positive HIT test (usually ELISA for heparin-platelet factor IV anti-bodies), rebound of platelets after cessation of heparin; coagulation times usually normal; PT normal (aPTT may be prolonged due to heparin)

PT prolonged, aPTT normal or slightly prolonged, normal platelet count

Liver

PT and aPTT prolonged, platelets (moderately) low, insufficiency


dic with hyper-fibrinolysis with severe bleeding.
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