Introduction
Disseminated intra-vascular coagulation (DIC) is a complex pathological process associated with widespread intra-vascular fibrin deposition due to in vivo thrombin generation that overwhelms physiological inhibitors of coagulation. The various events occurring in DIC are depicted in Fig. 1. DIC is always secondary to an underlying disorder (Fig. 2). The clinical manifestations of DIC vary from mild to severe. In severe form the patients suffer from simultaneous occurrence of bleeding and thrombotic manifestations causing multiple organ failure. Such a situation poses a difficult problem for clinicians and sometimes confusion in taking therapeutic decisions.

Fig. 1: Events occurring in disseminated intra-vascular coagulation

* Some underlying diseases (sepsis and poly trauma) in addition to generation of thrombin also cause impairment of natural anticoagulants and insufficient removal of fibrin deposits contributing to amplification of fibrin deposits in microcirculation.

IV - intravenous. MAHA - microangiopathic haemolytic anaemia
Recent literature and few randomized controlled trials published, however have led to newer insights in understanding the pathophysiology of DIC and more objective therapeutic choices.

**Advances in Pathophysiology**

Studies published in past few years have changed some of the traditionally thought concepts of alterations in haemostatic mechanisms involved in DIC. Three important pathogenetic mechanisms (Fig. 3) that cause widespread intra-vascular fibrin deposition are:

1. **Generation of tissue factor that initiates in vivo coagulation.**
2. **Down regulation (suppression) of physiological anticoagulants.**
3. **Down regulation (inhibition) of fibrinolysis.**
   1. **Role of tissue factor in DIC**: Tissue factor plays a dominant role in initiation of fibrin deposition in DIC. Studies by Pixley\(^1\) and Levi\(^2\) in animal models have demonstrated...
thrombin generation in DIC is solely mediated by the extrinsic pathway involving tissue factor and activated factor VII (VIIa) and not through involvement of both intrinsic and extrinsic pathways as thought hitherto. Investigations in patients with septicemia confirm that endotoxin and cytokines (IL-6) induce tissue factor expression in circulating monocytes.  

2. Suppression of physiological anticoagulants: Down regulation of physiological anticoagulation system contributes to exaggeration of the process of fibrin deposition initiated by tissue factor. All three major physiological anticoagulants i.e. anti thrombin (ATIII), protein C (PC) and tissue factor pathway inhibitor (TPFI) are defective in DIC. Low levels of AT III (as low as 30%) have been shown in severe sepsis. It is considered to be an indicator of poor prognosis. Replacement of AT III in experimental DIC in baboons has been shown to block systemic activation of coagulation and reduction in mortality. Anti thrombin III regulation of thrombin activity fails in DIC because of many factors including consumption of ATIII, degradation by enzymes released from activated neutrophils, extravascular leakage and impaired hepatic function in sepsis. Impairment of protein C system in DIC is cytokine mediated. Particularly high levels of TNF alpha result in down regulation of thrombomodulin on endothelial cells. Other factors contributing to protein C impairment are enhanced consumption, vascular leakage and impaired liver synthesis. Animal studies have demonstrated that administration of activated protein C controls DIC and improves survival. Involvement of TFPI pathway in DIC is contemplated due to studies reporting alterations in TFPI levels in DIC and administration of recombinant TFPI in endotoxin induced DIC resulted in complete inhibition of DIC TFPI.

3. Inhibition of fibrinolysis: Evidence suggests that inhibition of fibrinolysis occurs in DIC and not an increase in fibrinolytic activity as formerly believed. Increased fibrinolytic activity contributes further propagation of fibrin deposit. Yamamoto reported lack of fibrin thrombi in kidneys of plasminogen activator inhibitor (PAI-1) knockout mice challenged with endotoxin. This can be explained on the basis that the initial fibrinolytic response occurring in endotoxaemia is immediately followed by suppression of fibrinolytic activity because of increase in plasma levels of PAI-1. Increased fibrinolytic activity contributes further propagation of fibrin deposit.

Management of DIC
Management of DIC involves following three important steps, which should be initiated timely and sequentially.

I. Vigorous therapy underlying disorder.
II. Energetic treatment of life threatening complication e.g. shock, hypoxaemia, and acidosis.
III. Therapy of DIC per se.

The success or failure of management largely depends on effective therapy for underlying disease. In some patients DIC resolves after successful therapy of underlying cause e.g. abruptio placentae, dead fetus syndrome. In such cases no further treatment is required unless the consumption process has produced bleeding and or thrombotic manifestations, where as in situations like sepsis, poly trauma, snake bite etc, the intra-vascular coagulation persists and these patients require supportive treatment till complete cessation of DIC and restoration of organ damage.

Therapy of DIC Per Se
I. Replacement of blood components.
II. Use of heparin and other anticoagulants.
III. Restoration of anti coagulant pathways.
I. Replacement of blood components

Thrombocytopenia (platelet count < 50,000/cmm) and depleted coagulation factors may produce bleeding manifestations such as ecchymosis, bleeding from surgical wound, bleeding from mucus membranes, bleeding in vital organs such as brain and liver. Restoration of platelets is achieved by infusion of platelet concentrates (generally random donor platelet concentrate are used). For restoration of coagulation factor deficiencies infusion of fresh frozen plasma or cryoprecipitate (as a source of fibrinogen) are used. The decision to initiate and continue of replacement therapy should not be based on the basis of results of laboratory tests alone. It is indicated only in patients with bleeding or those who are at high risk of bleeding diathesis. There are no randomized trials addressing dosage schedules, efficacy of therapy with platelets and fresh frozen plasma, cryoprecipitate however guidelines regarding there usage is given in Fig. 4 may be of use in practice.

II. Use of heparin and other anticoagulants:

In small uncontrolled studies heparin use in DIC has been shown to be beneficial but these results have not been substantiated in controlled clinical trials. Heparin is given in dose of 5-10 U/kg by continuous intravenous infusion Although safety of heparin is debatable in bleeding DIC patients, its use in doses mentioned above have not been shown to be associated with significant increase in bleeding complications. Low molecular weight heparin may be used as alternative to unfractionated heparin. Heparin is indicated in DIC if (A) replacement of blood components alone does not control bleeding or achieve haemostatic levels of platelets and coagulation factors as indicated by improvement in platelet count and partial thromboplastin time. (B) evidence of predominant micro and/or macro vascular thrombosis e.g. acral ischaemia, purpura fulminans. (C) evidence of venous thromboembolism (D) prior to evacuation of dead fetus. Recently some of the newer agents under going Phase II/III trials are (A) Inactivated factor VIIa (B) recombinant NAPc2 derived from nematod anticoagulant protein. (C) recombinant tissue factor pathway inhibitor.

III. Restoration of anticoagulant pathways:

(A) Use of AT III concentrate: Initial randomized controlled trials using AT III concentrate in DIC in sepsis and/or shock demonstrated improvements in laboratory parameters and shortening of duration of DIC. However in another multicentric, randomized controlled trial, with the use of AT III in patients of severe sepsis, the difference in the mortality was not found to be statistically significant.

(B) Use of protein C concentrate: Administration of protein C has been shown to ameliorate coagulation abnormalities in DIC. A phase III trial of activated protein C concentrate in patients with sepsis was prematurely stopped because efficacy in reducing mortality in these patients. This is the first intervention shown to be effective in reducing mortality in severely septic patients. Use of recombinant human activated protein C has been recently approved by US FDA and European community for patients with severe sepsis.

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**Component** | **Aim** | **Dose**
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Platelet concentrate | Platelet count | 1 donor unit / 10 Kg
Cryoprecipitate | Fibrinogen level | Approximate 3 gm fibrinogen in Adults
Packed Red Blood cell | Hemoglobin | >8gm/dl

Fig. 4 : Blood Components used in disseminated intra-vascular coagulation
References


