Disseminated intravascular coagulation (DIC) is a syndrome characterized by systemic activation of coagulation and fibrinolytic systems, leading to widespread microvascular thrombosis, causing ischemic multi organ dysfunction. Simultaneously there is ongoing consumption of platelets, coagulation factors and natural anticoagulants leading to bleeding. DIC is always secondary to underlying disorder which causes activation of coagulation and inflammatory pathways.

**PATHOGENESIS**

The major physiological abnormalities leading to DIC may be described as follows:

- Initiation and propagation of procoagulant pathways
- Impairment of natural anticoagulant systems
- Dysregulated endogenous fibrinolysis
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**Pathogenesis**

The major physiological abnormalities leading to DIC may be described as follows:

- Initiation and propagation of procoagulant pathways
- Impairment of natural anticoagulant systems
- Dysregulated endogenous fibrinolysis
- Platelet activation and fibrin deposition
- Activation of systemic inflammation

The physiological derangements in DIC are mediated by cytokines like Interleukins(IL1, IL6), TNF alpha and NET (Neutrophil extracellular traps). Thrombin generation is initiated by tissue factor/Factor VIIa pathway. Tissue factor is expressed by malignant cells in leukemias, solid tumors; endothelial cells and activated monocytes in sepsis. Tissue factor is also released during trauma, burns, head injury and from placental site in obstetrical causes leading to DIC. Natural anticoagulants like TFPI (Tissue factor pathway inhibitor), Protein C, Protein S and Antithrombin are significantly reduced. Fibrinolytic system is either hypofunctional or markedly active depending on the etiology. Severe endothelial injury occurring in sepsis and trauma can trigger DIC.

DIC may arise in the setting of various etiologies as listed in table:

![Regulatory pathways of hemostasis and pathogenesis of DIC. (APC, Activated protein C; APL, acute promyelocytic leukemia; ATIII, antithrombin III; HCII, heparin cofactor II; prothrombinase complex, membrane complex of factors Xa and Va and prothrombin; PS, protein S; tenase complex, membrane complex of factors IXa, VIIIa, and X; TF, tissue factor; TF-FVIIa, tissue factor VIIa complex; TFPI, TF pathway inhibitor; TM, thrombomodulin; tPA, tissue plasminogen activator).](image-url)
Conditions associated with DIC:

1. Sepsis and severe infection
2. Trauma
3. Organ destruction e.g. pancreatitis
4. Malignancy
   - Solid tumours (metastatic adenocarcinoma)
   - Leukaemia (AML M3 & M5, ALL)
5. Obstetric causes
   - Amniotic fluid embolism
   - Placental abruption
   - Pre-eclampsia
6. Vascular abnormalities
   - Large haemangiomia
   - Vascular aneurysm
7. Severe liver failure
8. Toxic and immunological insults
   - Snake bites
   - Recreational drugs
9. ABO transfusion incompatibility
10. Transplant rejection

DIC occurs in 35% cases with severe sepsis including Gram +ve, Gram -ve, falciparum malaria, fungal and parasitic infections and haemorrhagic fever. Inflammatory cytokine and Neutrophil extracellular trap mediated DIC in sepsis is triggered by bacterial components like lipopolysaccharide, lipoteichoic acid and exotoxins. Microvascular thrombosis causing organ failure predominates in sepsis associated DIC, doubling the mortality rate in sepsis. DIC complicates acute leukemias (AML M3 & M5), lymphoproliferative disorders and solid tumors in approximately 20% cases. Metastatic adenocarcinomas are associated with chronic DIC. Acute promyelocytic leukemia is associated with hyperfibrinolytic type of DIC.

**TYPES OF DIC:**

Depending upon the predominant pathogenetic mechanisms of DIC the disease is classified into four types.

1. **Bleeding type:** Bleeding is the primary symptom. The vector of hyperfibrinolysis dominates. Eg: APML, obstetric causes, aortic aneurysm.

2. **Organ failure type:** Vector of hypercoagulation dominates. Organ dysfunction is the main symptom. (Hypercoagulation type). Eg: sepsis. Lipopolysaccharide and cytokines cause elevated levels of PAI (plasminogen activator inhibitor) leading to suppression of fibrinolysis and widespread microvascular thrombosis.

3. **Massive bleeding type (Consumptive type):** Both the vectors (hypercoagulation & hyperfibrinolysis) are strong. Major bleeding is the main symptom. Seen in patients with major bleed after surgery or obstetric causes.

4. **Pre DIC or asymptomatic DIC:** Here both the vectors are weak. There are no clinical symptoms even though there are laboratory abnormalities.

**CLINICAL PRESENTATION:**

Widespread mucocutaneous bleed predominates the clinical picture. Major bleed occurs only in 5-12%. Microvascular thrombosis with organ failure is more common; reported in 40% cases with sepsis and 10-15% cases
with trauma or malignancy. Hence DIC should be suspected in critically ill patients with unexplained dysfunction of skin (70%), kidneys (50%), lungs (50%), liver (35%), adrenal (30%), heart (20%), brain etc. Acral gangrene, purpura fulminans are rare manifestations.

LABORATORY DIAGNOSIS:

There is no single test which can establish the diagnosis of DIC. In the background of appropriate clinical setting, if laboratory tests are supportive diagnosis of DIC is made.

Screening coagulation tests: PT, APTT, platelet count.

PT and APTT are prolonged in 50-60%; may be normal in some cases. This is due to the presence of circulating activated clotting factors Factor Xa or thrombin. Hence normal PT and APTT does not always rule out DIC. In suspected cases, serial monitoring should be done. PT, not INR is to be monitored. Thrombin time helps to exclude heparin contamination in patients with prolonged APTT.

Platelet count: Thrombocytopenia is the most common laboratory abnormality, occurring in 98% cases. PLC < 50,000/mm3 is seen in 50% cases. Most important cause of thrombocytopenia is thrombin induced platelet aggregation. Continuous drop in platelet count even if within normal limits signifies platelet consumption.

Fibrin degradation products: Increased in 85-100% cases with DIC. Elevated FDP signifies thrombin formation and enhanced fibrinolytic activity. FDP assay may be done using ELISA technique or latex agglutination assay which measures D& E fragments of fibrinogen. Drawback of FDP assay is that it does not distinguish between cross linked fibrin & fibrinogen degradation. FDP is not specific for DIC. May be negative in early DIC or advanced DIC. Hence negative test do not rule out DIC.

D dimer: D dimer is a specific FDP, formed by plasmin activity on cross linked fibrin. It is estimated by Latex agglutination test using monoclonal antibody against D dimer neo antigen DD 3B6/22- specific for cross-linked fibrin derivatives containing D dimer configuration. Elevated D dimer level is seen in trauma, recent surgery, venous thromboembolism, liver and kidney dysfunction.

Soluble fibrin monomer (SFM): Serves as a marker for both pro coagulant and plasmin activation. Both D dimer and soluble fibrin monomer can be estimated by ELISA. SFM is generated only intravascular, hence not influenced by inflammation and trauma. But the major problem is related to quantification; discordance is reported among various assay systems.

Fibrinogen: Fibrinogen is an acute phase reactant. Hence level can remain high, even though we expect low levels in DIC. Sensitivity is only 28%. Factor VII levels can also remain high as a part of acute phase reaction in DIC.

Peripheral smear: Fragmented RBCs constitute < 10% of total RBC in peripheral smear in cases with DIC. If seen in increased numbers, consider other causes of thrombotic microangiopathy like TTP or HUS. Peripheral smear examination for schistocytes will be helpful in chronic DIC where coagulation tests may be normal. Here fragmented RBCs may be
the only finding suggestive of DIC. RBC fragmentation occurs due to microvascular thrombotic occlusion causing mechanical damage to RBCs.

**NEWER MARKERS IN DIC**
- Increased soluble thrombomodulin
- Increased amount of histones and extracellular deoxyribonucleic acid
- Increased high-mobility group box protein-1
- Neutrophil activation in the form of neutrophil extracellular traps
- Decreased ADAMTS-13
- Complement markers (C3, membrane attack complex, and mannose-binding lectin)
- Presepsin (soluble cluster of differentiation 14 subtype)
- Increased plasminogen activator inhibitor
- Increased vWFpropeptide
- Atypical light transmittance profile on APTT (Biphasic wave form)

Laboratory Features of Chronic DIC:
- Platelet count: normal or borderline
- Fibrinogen: normal/increased
- PT & APTT: normal/supernormal
- Schistocytes: seen 90% patients, most important clue to chronic DIC.
- FDP: usually increased
- Fibrinopeptide A: usually increased
- D dimer: usually increased

**SCORING SYSTEM FOR DIC:**

A simple scoring system was developed by ISTH (International society of thrombosis and hemostasis) for the diagnosis of DIC. The ISTH scoring system should be used only in the presence of an underlying disorder known to be associated with DIC.

Sensitivity of DIC score is 93% and specificity is 98%. Scoring is based on Platelet count, PT, fibrin related markers (usually D dimer and fibrinogen. Score >5 is suggestive of overt DIC. Score <5 is indicative (not affirmative ) of Pre DIC(Non overt DIC, a stage where DIC is still reversible if underlying disease is controlled). The severity of DIC according to this scoring system is a strong predictor of mortality in sepsis. Similar scoring systems have been devised by Japan, Italy and UK.

**SCORING ALGORITHM FOR DIAGNOSIS OF DIC:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count, x109/L = score</td>
<td></td>
</tr>
<tr>
<td>&gt;100 = 0</td>
<td></td>
</tr>
<tr>
<td>&lt;100 = 1</td>
<td></td>
</tr>
<tr>
<td>&lt;50 = 2</td>
<td></td>
</tr>
<tr>
<td>Level of fibrin markers (eg D-dimer, fibrin degradation products) = score</td>
<td></td>
</tr>
<tr>
<td>No increase = 0</td>
<td></td>
</tr>
<tr>
<td>Increased but (&lt;5 times upper limit of normal) = 2</td>
<td></td>
</tr>
<tr>
<td>Strong increase (≥5 times upper limit of normal) = 3</td>
<td></td>
</tr>
<tr>
<td>Prolonged prothrombin time* = score</td>
<td></td>
</tr>
<tr>
<td>&lt;3 s = 0</td>
<td></td>
</tr>
<tr>
<td>≥3 s but &lt;6 s = 1</td>
<td></td>
</tr>
<tr>
<td>≥6 s = 2</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen level</td>
<td></td>
</tr>
<tr>
<td>&gt;1.0 g/L = 0</td>
<td></td>
</tr>
<tr>
<td>≤1.0 g/L = 1</td>
<td></td>
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</tbody>
</table>

This scoring system is only appropriate in patients with an underlying disorder that can be associated with DIC. A score of ≥5 points is compatible with DIC. If the score is <5, consider repeating after 1 to 2 days. If prothrombin time values are only available as INRs, an INR value of 1.3 or 1.5 will generate 1 or 2 points, respectively.

**TREATMENT:**

Treatment of the underlying condition is the cornerstone of management; DIC
spontaneously resolves if the primary disease is treated. This is true for organ failure, bleeding and non-symptomatic DIC. Blood product support is needed in massive bleeding type DIC.

**BLOOD PRODUCT SUPPORT:**
Threshold for transfusion depends upon the clinical status of the patient. Blood product support is mainly used in patients with bleeding or massive bleeding type of DIC who are actively bleeding or at high risk of bleeding.

Platelet concentrate is used in patients who are actively bleeding or at high risk of bleeding (post-operative patients, invasive procedures) if the platelet count is <50,000/mm³. In non-bleeding patient, platelet concentrate is transfused with a threshold of 10,000-20,000/mm³.

Fresh frozen plasma (FFP) : FFP transfusion is used in actively bleeding patient or if the PT or APTT is >1.5 times the normal value or fibrinogen <1.5g/dl. Initial dose of 15ml/kg of FFP is used. A higher dose of 30ml/kg provides a more complete correction of coagulation abnormalities.

Cryoprecipitate or fibrinogen concentrate may be used in actively bleeding patient with persistent severe hypofibrinogenemia <1.5g/dl despite of FFP transfusion. Prothrombin complex concentrate (PCC) may be considered in actively bleeding patient if FFP transfusion is not available. But PCC lacks many factors like Factor V, protein C, protein S etc. Efficacy and safety of activated Factor VII a (rFVIIa) in DIC patients with life threatening bleed is unknown; hence it should be used only in the setting of clinical trials.

**ROLE OF ANTICOAGULANTS :**
Anticoagulants are used in the following context in DIC

1. Therapeutic doses of heparin (LMW heparin preferred over UFH) if thrombosis is a predominant manifestation.

2. Overt thromboembolism or organ failure (Purpura fulminans): LMW heparin preferred over UFH heparin in patients with high bleeding risk and dialysis dependent acute renal failure. Monitoring should be done with anti F Xa levels, since APTT will be prolonged already.

3. Venous thromboembolism prophylaxis with LMW heparin or UFH in prophylactic dose is recommended in critically ill non bleeding patients with DIC who are at high risk of VTE.

But there are no randomized trials which demonstrate improved survival outcomes with use of heparin In DIC.

**ANTIFIBRINOLYTICS :**
 Generally anti fibrinolytics are not recommended in DIC. But it may be used in hyper fibrinolytic type of DIC. Classical example is trauma associated DIC, APML and Caprosate where antifibrinolytics may be used in early phases. Tranexamic acid will assist in the formation of well-organized fibrin clot. Once the initial hyperfibrinolysis phase passes, further fibrin clot is not disturbed by brisk fibrinolysis and the vector shifts towards thrombosis, when antifibrinolytics are not needed. In DIC caused by sepsis, fibrinolysis is limited and microvascular thrombosis dominates the clinical picture. Hence antifibrinolytics are contraindicated here.
Vitamin K supplementation may be done if deficiency is suspected.

**NATURAL ANTICOAGULANTS:**

1. Antithrombin was one of the natural anticoagulants earlier studied in DIC. Antithrombin levels decrease early in DIC and it is associated with increased mortality. Results of KyberSepttrria (JAMA 2001) did not show any survival benefit for antithrombin over placebo in patients with sepsis & DIC.

2. Activated protein C (APC) was a landmark innovation in the management of DIC associated with sepsis after the results of PROWESS (Protein C worldwide evaluation in severe sepsis) trial was published. But subsequent several trials (ADDRESS, RESOLVE, ENHANCE, PROWESS SHOCK) showed no difference in survival with APC; rather there was an increase in the incidence of severe bleed with APC. Based on these data, FDA approval for Activated protein C in DIC was withdrawn in 2011.

3. Soluble thrombomodulin: Soluble thrombomodulin is the most recent development in the management of DIC. Efficacy was proven in DIC related to infection and malignancy in multicentric RCT ART123. DIC resolution rate in thrombomodulin arm was 66.1% against 49.6% in heparin group. 28 day mortality was also lesser in the thrombomodulin arm (38%) Vs 34.6% in the heparin arm. Thrombomodulin has anti-inflammatory effects, suppress complement activation and inhibit leukocyte endothelial cell interaction.

**CONCLUSION:**

1. Maintain high index of suspicion of DIC in all critically ill patients with organ dysfunction and/or bleeding or unexplained laboratory abnormalities.

2. Use of the DIC scoring system helps in making the diagnosis and predicting prognosis.

3. Judicious use of blood products according to the bleeding profile is recommended.

**REFERENCES:**


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