CHAPTER

29

Disseminated Intravascular Coagulation

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Introduction

Disseminated intravascular coagulation (DIC) is an acquired hypercoagulable state, induced by the progressive generation of thrombin in circulation. It is a pathophysiologic term describing a continuum of events that occur in the coagulation pathway as a complication of many different serious and life-threatening disease states. The International Society on Thrombosis and Hemostasis has suggested the following definition for DIC: "An acquired syndrome, characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction.[1] DIC occurs in acute and chronic forms. In its acute (overt) form it is a hemorrhagic disorder, characterized by multiple ecchymoses, mucosal bleeding and consumption of platelets and clotting factors. Chronic (nonovert) DIC, on the other hand, is more subtle and involves venous thromboembolism (VTE) accompanied by evidence of activation of the coagulation system and is associated with conditions like malignancies and intrauterine death of fetus. With chronic DIC, coagulation factors may be normal, increased, or moderately decreased, as may the platelet counts.[2]

The syndrome can be considered to involve a 2 phase phenomenon: a hypercoagulable phase that leads into a hypocoagulable phase manifesting in bleeding. Most physicians encounter patients in the hypocoagulable state with bleeding manifestations in critical illnesses. The thrombotic complications are more frequently seen in patients with malignancies who run a chronic course. In acute promyelocytic leukemia the patient usually presents with bleeding tendency secondary to DIC triggered by the granules released from the promyelocytes.

DIC is initiated by the activation of the clotting cascade, mainly the tissue factor (TF) pathway. Diagnosis of DIC can be difficult, depending upon the phase in which a diagnosis is attempted, since many laboratory parameters can be normal in the hypercoagulable phase except for a falling platelet count. The diagnosis of the hypocoagulable phase is easier, as the patient manifests clinical bleeding with abnormalities in global coagulation parameters.

DIC is seen in association with a number of well-defined clinical situations, including sepsis, major trauma, and abruptio placenta with laboratory evidence of the following[1]

- Activation of procoagulant pathway
- Activation of fibrinolytic pathway

- Inhibitor (natural anticoagulants) consumption
- Evidence of end-organ damage or failure

Though numerous laboratory tests are available to monitor DIC, most patients are managed successfully using only routine screening tests, platelet counts and assays for fibrinogen and D-dimer. Treatment of DIC should focus on reversing the underlying disorder initiating the coagulopathy. Supportive care with appropriate blood components is paramount to minimise the mortality and morbidity. By and large, the outcome of DIC is dictated by the severity of the underlying disorders leading to DIC and how successfully they can be managed. Novel treatments are being investigated for treating DIC, many of which target the excessive TF activity that characterizes DIC.

Frequency

- DIC may occur in 30-50% of patients with sepsis with equal frequency in gram negative and positive bacterial infections. In patients with severe trauma who have a systemic inflammatory response syndrome, DIC can occur in 50-70% patients, particularly in patients with neuro-trauma. In obstetrical patients with abruptro placentae, septic abortions and amniotic fluid embolism, DIC occurs in more than 50% patients. Cancer patients with metastatic tumors have DIC in approximately 10-15% patients and it occurs in 15% cases with acute leukemia with highest frequency in APML.[1]
- Incidence of DIC varies with the energy with which the diagnosis is pursued. High index of clinical suspicion is warranted in a clinical setting for DIC. The incidence is 1:1000 admissions in a general hospital. Most of these data is from the West and there is a need to generate epidemiological data from India.

Morbidity / Mortality

Morbidity and mortality depend on both, the underlying disease and the severity of coagulopathy. The mortality rates in different diseases complicated by DIC is as under:

- Septic abortion with shock due to clostridial infection associated with severe DIC has a mortality rate of 50%.
- In major trauma, the presence of DIC approximately doubles the mortality rate.
- Idiopathic purpura fulminans associated with DIC has a mortality rate of 18%.

Sex: Incidence is equal in males and females.

Age: No age predilection is known.

Pathogenesis

The pathogenetic pathways of DIC have been largely clarified by recent studies in animal models and humans. DIC occurs when monocytes and endothelial cells are activated by toxic substances elaborated in the course of certain diseases. These cells generate TF, which in turn activates the coagulation cascade generating thrombin. Thrombin leads to systemic formation of fibrin.[3] Simultaneously, there is consumption of naturally occurring anticoagulants and a delayed removal of fibrin due to impairment in the fibrinolytic pathways. Several pro-inflammatory cytokines play a pivotal role in the causation of systemic inflammatory response. The principal cytokines involved appears to be interleukin -6, interleukin -1β and tumor necrosis factor-α which are active in both polytrauma and sepsis.[4]

Thrombin is generated predominantly by the extrinsic pathway (involving tissue factor and activated factor VII) the inhibition of which totally suppressed endotoxin induced thrombin generation in animal models. However, interference with the intrinsic pathway did not in anyway affect activation of coagulation.[4]

There is a decrease in the levels of all major physiological anti-coagulants like anti-thrombin III, protein C and tissue factor pathway inhibitor (TFPI). Anti-thrombin III which is the most potent thrombin inhibitor, is markedly reduced due to consumption, impaired synthesis and degradation

Table 1 : Conditions underlying DIC syndrome

Infections
Acute DIC: Bacteria and their toxins, fungi, viruses, rickettsiae
Chronic DIC: Chronic infection. e.g., tuberculosis, abscesses, osteomyelitis
Obstetrical complications
Acute DIC: Abruptio placentae, abortions (especially therapeutic and septic abortions), amniotic fluid embolism, hemorrhagic shock
Chronic DIC: Dead fetus syndrome
Trauma
Acute DIC: Polytrauma; neurotrauma
Venoms
Acute DIC: Snake bites and rarely spider bites
Malignancy
Acute DIC: Acute promyelocytic leukemia, acute myelomonocytic or monocytic leukemia, disseminated prostatic carcinoma
Chronic DIC: Gastrointestinal, lung and breast malignancy
Vascular disease
Acute DIC: Brain infarction or hemorrhage
Chronic DIC: Aortic aneurysm, giant hemangioma
Noninfectious inflammatory diseases
Inflammatory bowel disease: Crohn's disease and similar disorders
Others
Acute DIC: Heparin-induced thrombocytopenia with thrombosis (HITT); purpura fulminans in newborns (homozygous protein C deficiency); transfusion of ABO incompatible red cells.

by elastase released from activated neutrophils. The decrease in total protein-C levels is caused by consumption and impaired synthesis. The fibrinolytic system is suppressed at the time of maximal activation of coagulation. This inhibition is caused by a sustained increase in the levels of plasminogen activator inhibitor type -1 (PAI-1). Though secondary fibrionolysis occurs in response to fibrin formation, its activity is too low to counteract systemic deposition of fibrin.

Clinical Features

In addition to the symptoms related to the underlying disease, ascertain history of blood loss such as gastrointestinal bleeding and hypovolemia. Fresh bleeding from the percutaneous intravenous catheter sites in an ICU patient with mucocutaneous bleeds should always raise the possibility of DIC in the ICU setting. Look for symptoms and signs of thrombosis in large vessels, such as DVT, and of microvascular thrombosis, such as renal failure. Bleeding from at least 3 unrelated sites is particularly suggestive of DIC. Patient can present with varied symptoms due to affection of any organ in the body. The common presentation include.

- Skin ecchymosis, bleeding from I/V sites, endotracheal tubes and urinary catheters
- Gingival bleeding, epistaxis
- Cough, dyspnea
- Confusion, disorientation
- Fever

Acute and Chronic DIC

Acute DIC is the most commonly seen form in clinical practice and presents with bleeding manifestations from various sites. It is a hematological emergency and is rapidly progressive because of explosive generation of thrombin. Prothrombin time (PT) and activated partial thromboplastin time (APTT) are prolonged along with hypofibrinogenemia and thrombocytopenia. FDP and D-Dimer levels are increased.

Chronic DIC is less explosive as there is time for compensatory responses to take place. Usually presents with features of hyper-coagulable state with or without VTE. Platelet levels are low along with raised levels of FDP and D-Dimer. PT and APTT may be normal or mildly prolonged. APTT may be shortened in the hyper-coagulable phase.

Conditions Associated with DIC

The conditions that regularly give rise to the DIC syndrome are outlined in Table 1. A high index of clinical suspicion in a given setting helps anticipate onset of DIC with timely intervention by the physician.

Differential Diagnosis

A number of clinical disorders can result in acquired bleeding diathesis and hemostatic laboratory abnormalities and needs to be distinguished from DIC. Some of these common conditions are as under.

1. **Liver Disease and DIC**

   Patients with advanced liver disease are prone to a number of hemostatic and thrombotic derangements. The various factors responsible for these are altered hepatic synthesis of coagulation factors, fibrinolytic proteins and natural inhibitors. Besides this the patients have impaired renal clearance of these activated proteins. Portal hypertension leads to splenomegaly with enhanced platelet sequestration and thrombocytopenia. The tests reflecting thrombin generation such as Protamine paracoagulation assay, the prothrombin fragment 1.2, thrombin-antithrombin (TAT) complex levels and D-dimer levels may help exclude liver disease. Factor VIII levels will be normal in liver disease without DIC.

2. **Thrombotic Micro-angiopathies (TMA)**

   These should be suspected when patient has a classical picture of TMA e.g, microangiopathic hemolytic anemia (MAHA), neurological manifestations, fever, thrombocytopenia and renal dysfunction or at least three out of these (MAHA, neurological symptoms and thrombocytopenia). It resolves rapidly after child birth and usually does not recur.

   HELLP(hemolysis with elevated liver enzymes and low platelets) syndrome is a TMA seen in 20% patients with pregnancy and severe pre-eclampsia. More common in multiparous women and 70% cases occur before 27 weeks of gestation. This is a multisystem disorder characterized by MAHA, hepatic dysfunction, raised LDH levels and thrombocytopenia. In its severe form DIC can also occur.

3. **Fibrinogenolysis**

   This condition presents with bleeding diathesis and is caused by severe liver disease, puerperium, post CABG and in disseminated neoplasm. It is characterized by hypo-fibrinogenemia, prolonged PT & APTT with elevated FDP. However, the platelet counts and D-Dimer levels are normal. Management involves treatment of the underlying cause, use of anti-fibrinolytic (tranexamic acid) agents and supportive care with cryoprecipitate to replenish fibrinogen levels.

4. **Disorders of Hemostasis**

   At times, acquired disorders of coagulation may mimic a picture of DIC but the clinical profile and laboratory parameters (correctible factor deficiency) differentiate hemostasis related disorders from DIC.

   Vitamin K deficiency is seen after prolonged antibiotic therapy, malnutrition and liver disease. It can present with the bleeding diathesis with abnormal coagulation profile. However, D-Dimer levels will be normal.

5. **Thrombocytopenia**

   It can result from bone marrow failure syndromes, immune destruction or systemic illnesses. Laboratory results can easily differentiate between these. It is important to differentiate thrombocytopenia, secondary to bone marrow involvement from that due to DIC. In thrombocytopenia due to DIC, glycocalicin (released from degraded GP1b/IX complex) levels are raised. Platelet activating factor, released from neutrophils and endothelial cells in acute inflammatory diseases, is raised and correlates inversely with platelet counts.

Laboratory Studies

No single laboratory test is diagnostic of DIC. A clinical setting, wherein, DIC is known to occur along with a combination of screening and confirmatory tests helps in arriving at a

diagnosis of DIC. It involves tests for thrombin and plasmin generation and screening tests for hemostatic function that delineate the severity of coagulation factor consumption. Although abnormalities in the screening assays such as the PT, a PTT or platelet count may provide important corroborative evidence of hemostatic component consumption, the diagnosis of DIC should not be made without at least one positive test indicative of excessive of thrombin generation (Table 2). The two most readily available tests that document the excess activity of thrombin are immunoassays for D-dimers and protamine Para coagulation assay for fibrin monomer.[5]

Laboratory diagnosis consists of 2 stages: (1) Screening assays and (2) Confirmatory assays.

The Screening Tests

The common screening tests used to diagnose DIC are

- Prothrombin time (PT),
- Activated partial thromboplastin time (a PTT),
- Platelet count,
- Fibrinogen level.

If 2 of these tests are abnormal, diagnosis is possible; if 3 tests are abnormal, diagnosis is probable if all tests are abnormal, diagnosis is most likely. The scoring system for DIC mentioned earlier is useful in arriving at a diagnosis of DIC.[2]

Occasionally the snakebite of rattle snake (*Crotalus horridus*) will lyse fibrinogen and aggregate platelets but will not cause DIC because there is no increased thrombin or plasmin formation. In these patients, if one measures all coagulation factors, they are within normal range.

Confirmatory Tests

These provide objective evidence of simultaneous thrombin and plasmin generation and are listed in Table 2. D-dimers are the proteolytic by-products of plasmin degradation of cross-linked fibrin polymers. The formation of D-dimers requires prior formation of fibrin monomer, which is cross-linked by F XIIIa.[6]

The D-Dimer Test

D-dimer is very sensitive test for the diagnosis of DIC and has a high negative predictive value of > 90% (normal value 0.2 to 0.5 μg/ml; cutoff values varies with the type of assay kit)[7]. It detects plasmin-cleaved, insoluble, cross-linked fibrin. A positive test confirms the formation of both thrombin and plasmin, making it a powerful diagnostic test for DIC. Thrombin cleaves fibrinogen to liberate fibrinopeptides A and B, leaving fibrin monomer. Thrombin also activates factor XIII to induce soluble fibrin monomer to interact end-to-end and side-to-side, causing it to become cross-linked, making the soluble protein insoluble.[5] When plasmin forms, it cleaves insoluble, cross-linked, fibrin monomer that is held together by its D domains liberating a dimer of the D domain, which is measured by the antibody directed to this region. D-dimers may be falsely elevated in patients who have undergone recent surgery, trauma, renal, liver and cardiac failure.[6] Therefore, patients with D-dimer level < 0.5 μg/ml should not be diagnosed as having DIC unless there is other corroborative evidence.

The Fibrin Degradation Products (FDPs)

FDPs are a measure of plasmin-cleaved fibrinogen or fibrin. Fibrin/fibrinogen degradation products (FDP's) do not distinguish between the plasmin degradation by-product of either fibrin or fibrinogen. FDPs have a sensitivity of 85% and specificity of only 50% (normal value < 10 μg/ml). It is increased in DIC, primary fibrinolysis, hepatic & renal failure and post surgery. A combination of FDP and D-dimer has 100% specificity and sensitivity.

Other tests available but not routinely done are,

The **thrombin time** can be prolonged because of fibrinogen consumption.

Detecting **thrombin (TAT)** complexes in plasma suggests prior thrombin formation.

Plasma levels of factors V and VIII can be low in patients with acute and severe DIC. Normal or elevated levels do not exclude the diagnosis.

Table 2 : Lab tests in DIC

Screening assays for factor and platelet consumption
• Platelet count
• Prothrombin time (PT)
• Activated partial thromboplastin time (APTT)
• Thrombin time (TT)
• Quantitative fibrinogen assay
Laboratory markers of thrombin generation
• D-dimers
• Protamine paracoagulation assay for fibrin monomer
• Ethanol gel assay for fibrin monomers
• Fibrinopeptide A
• Prothrombin fragment 1.2
• Thrombin-antithrombin complex
Ancillary tests
• FDP'S
• Euglobin test
• Antithrombin levels
• Antiplasmin levels
• Factor V level

Schistocytes can be observed on a peripheral smear, although only in a minority of patients.

A useful scoring system to help diagnose DIC has been formulated by the International Society of Thrombosis and Hemostasis (Table 3). The scoring system is applied only if the patient has a clinical setting for DIC. This has to be done dynamically on a daily basis.

There are a large number of tests available to be done in DIC. However, in routine practice in most cases diagnosis of DIC can be made by demonstrating thrombocytopenia and schistocytes. (in a minority) along with prolongation of PT, a PTT and TT. Fibrinogen levels will be low.

Management of DIC

When there is no bleeding or VTE with only laboratory evidence of DIC, it is best to observe these patients without any replacement therapy and aggressively treat the underlying disease. No efforts should be spared to identify the underlying disease at the earliest.

Table 3 : Scoring system for overt Disseminated Intravascular Coagulation (DIC)[2]

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC?
If yes: Proceed.
If no: Do not use this algorithm.
2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, fibrin related marker)
3. Score global coagulation test results.
• Platelet count
(> 100 = 0; < 100 = 1; < 50 = 2) ☐
• Elevated fibrin related marker (e.g. D-Dimers; fibrin degradation products)
(no increase = 0; moderate increase = 2; strong increase = 3) ☐
• Prolonged prothrombin time
(< 3 sec = 0; > 3 but < 6 sec = 1; > 6 sec = 2) ☐
• Fibrinogen level
(>1.0 g/l = 0; < 1.0 g/l = 1) ☐
5. Calculate score ☐
If ≥ 5: compatible with overt DIC: repeat score daily
If < 5: suggestive (not affirmative) for non-overt DIC: repeat next 1-2 days.

In the presence of established DIC the cornerstone remains identification and aggressive management of the underlying cause accompanied by timely, appropriate supportive care. There may be difficulty in determining the extent of consumption of clotting factors and fibrinolysis in each case. Frequent monitoring of blood counts and coagulation parameters helps in optimising supportive care. Monitoring of circulatory volume status, gas exchange and electrolyte balance is also of paramount importance.

Prompt treatment of the underlying cause of DIC viz., optimal antibiotics in sepsis syndrome, uterine evacuation for abruptio placentae, restoration of hemodynamic stability for hypovolemic shock, antisnake venom for snake bite is considered the most important part of management.

Antibiotics

Antibiotics are started after taking blood cultures and is always administered intravenously. Careful

planning using the hospital infection committee guidelines to decide on the type of antibiotics used to treat the nosocomial infections will be an effective strategy. Outcomes are worse if the micro-organism is insensitive to the initial antibiotic regimens.

Component Support

Blood component support where indicated especially replacement of platelets and clotting factors minimises bleeding episodes. There is no truth in the old notion that blood component therapy adds "fuel to fire" theory.

Platelet Transfusion

Platelets should be maintained around 20-30,000 / cumm in a bleeding patient. In case there is major bleed or if there is an organ dysfunction a higher level may be required. One unit of random donor platelet raises the count by approximately 5000 - 8000/cumm assuming normal splenic pooling. Single donor platelet harvested by apheresis raises the platelet count by 20-40,000/ cumm. As far as feasible platelet should be of same blood group. Presence of fever, active bleeding and use of drugs like amphotericin will lower platelet counts.

Cryoprecipitate

Cryoprecipitate is rich in fibrinogen, factor VIII and vWF and is infused to maintain fibrinogen level > 100 mg/dL. The fibrinogen content of each unit varies from 100-250 mg depending upon processing techniques. Thus 1- 2 units/ 10 Kg can be given.

Fresh Frozen Plasma (FFP)

FFP provides all clotting factors and helps to correct PT/ APTT. It should be given in a dose of 10-15 ml/ kg every 8 to 12 hourly. Ideally PT/ APTT should be repeated 6 hourly at the onset of therapy, but tests done once a day in the morning as a routine may be sufficient. Transfusion can be stopped once lab parameters are corrected and clinical status improves.

Heparin

Use of heparin is a theoretically attractive proposition but it is practically used in very few situations. Heparin potentiates the naturally occurring plasma protease inhibitor, antithrombin, to inhibit thrombin, factor Xa, and other coagulation enzymes. In patients with adequate levels of antithrombin, the addition of heparin may increase the inhibitory activity of this protease.[8] Since heparin is a potent anticoagulant, it can itself, accelerate bleeding. Heparin probably is best reserved for patients who have self-limited evidence of digital ischemia and acral cyanosis and in chronic DIC with VTE. Heparin therapy is also useful in patients with purpura fulminans from protein C or S deficiency, a retained dead fetus and migratory thrombophlebitis. Its use in acute DIC is, controversial.

Indications

Chronic DIC of malignancy

Clinical thrombosis: dermal necrosis, purpura fulminans, acral ischemia, VTE

Retained dead fetus with hypofibrinogenemia

AML-M3 prior to conventional chemotherapy

In acute DIC when there is persistent bleeding and there is no rise in platelets or clotting factors despite adequate replacement therapy, implying ongoing consumptive coagulopathy, a trial of low dose of Heparin (300-500 U / hour) may be tried along with appropriate replacement therapy

Reduce the dose of heparin from that used for anticoagulation therapy for the management of DVT. Usually, heparin therapy is initiated without any loading dose as a constant infusion adjusting dose every 4 hours by 100-200 U/h. The decision to make an adjustment in the dose depends on the changes in the monitored parameters e.g. a rise or fall in platelet count, fibrinogen level, FDP and D-dimer levels. A rise in platelet counts and fibrinogen level is a sensitive marker indicating improvement in DIC status.

However, it is important to appreciate that heparin is less likely to improve outcome in the presence of ongoing DIC and can exacerbate bleeding in these patients.

LMWH is as effective in DIC as un-fractionated heparin providing reproducible anticoagulation with less frequent dosing. The incidence of heparin induced thrombocytopenia is much lower with use of LMWH.

Hence in nutshell heparin has very limited role in the management of DIC. Its use should be guided by institutional protocols.

Synthetic Inhibitors of Thrombin

In heparin induced thrombocytopenia (HIT) and when heparin is ineffective in the presence of antithrombin deficiency, these agents can be used as they directly inhibit thrombin. Antithrombin is not required for their action. It includes agents such as recombinant hirudin, desirudin, bivalirudin, argatroban, melagatran/ ximelagatran and dabigatran. The last two are oral agents. These drugs have a potential disadvantage as they do not have an antidote.

Anti-Thrombin Concentrates

Anti-thrombin concentrates neutralize thrombin, generated during DIC and potentially ameliorate thrombosis.[9,10] This effect is more understandable in presence of hepatic insufficiency. However, there is no improvement in mortality.

Activated Protein-C Concentrates

Activated protein C has been used in DIC associated with gram negative septicemia.[11] But its use in other situations is less well established. Further studies are needed to determine its utility in DIC.

Fibrinolysis Inhibitors

These act by blocking secondary fibrinolysis that accompanies DIC. The commonly used ones are tranexamic acid and aminocaproic acid. Under most circumstances these should not be used. They are useful in certain situations like: [12]

- When intense primary fibrinogenolysis can be demonstrated in association with disease states like acute promyelocytic leukemia.
- When patient is bleeding profusely, not responding to therapy even after components and heparin. Such a situation arises due to circulating FDP's.

Complications

Organ infarction and limb ischemia may occur. Renal, adrenal, and respiratory failure followed by multi-organ dysfunction may occur. More often death occurs due to infection or even uncontrolled bleeding.

Prognosis

The prognosis depends on the underlying disorder. If the condition is self-limiting then the prognosis is good. Aggressive approach towards antibiotic therapy is paramount as a delay in instituting appropriate antibiotics will have a negative impact on the outcome. The requirement for optimal blood component support can not be over emphasised. A team approach with good co-ordination between the hematologist, critical care team, laboratory services and the blood bank is most helpful. Prognosis is poor if there is:

- Failure to recognize the underlying etiology.
- Failure to understand that a good outcome is dependent on the nature of the underlying etiology, than on the DIC itself as illustrated by the following examples.
  - A patient with acute DIC that is associated with metastatic gastric carcinoma is likely to be fatal, regardless of treatment.
  - Alternatively, a patient with acute DIC associated with abruptio placenta needs quick recognition and obstetric treatment; the DIC resolves on treating the obstetrical catastrophe.

Conclusion

An awareness of the clinical setting in which DIC can occur and the diagnostic features that warn of its presence will help the physician to diagnose and treat DIC appropriately. Failure to do so can lead to development of complications of DIC which can be devastating. The focus

should be on treating the underlying cause of DIC accompanied by optimal supportive care for thromboembolic and bleeding complications. The prognosis depends on underlying cause and the stage of the disease. The role of newer agents remains to be defined.

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