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DISSEMINATED INTRAVASCULARCOAGULATION: AN PERSPECTIVE VIEW

Pathology

Mrs. Shilpa Sujit Kushte Ph.D. MLT Scholar Medical Laboratory Technology, Nims College of Paramedical Technology

Dr. Atul Khajuria Ph.D. Professor & H.O.D. Medical Laboratory Technology, Nims College of Paramedical Technology Nims University Rajasthan, Jaipur

Mr. Raju Ph.D. MLT (Pathology) Scholar, M.Sc. MLT (Pathology) Gold Medalist Medical Laboratory Technology Nims College of Paramedical Technology

ABSTRACT

Disseminated intravascular coagulation(DIC) is a life-threatening complication of several disease states. It can quickly lead to multi-organ failure and death, particularly if early recognition and treatment fail to occur. It is an acquired clinico biological syndrome characterized by systemic activation of the hemostasis and is provoked by several underlying disorders (sepsis, cancer, trauma, and pregnancy complicated with eclampsia or other calamities). DIC is a complex clinical syndrome with activation of the pro coagulant and fibrinolytic systems along with inhibitor consumption. Bleeding is a more common manifestation of DIC but most of the morbidity and mortality of DIC is due to microvascular thrombosis. The diagnosis and management of DIC is complex and challenging. The key is to address the underlying disorder that ultimately led to this condition developing. A reliable diagnosis of DIC can be made through simple scoring algorithms based on readily available routine hemostatic parameters. The clinical suspicion of DIC must be confirmed by laboratory tests and decreasing fibrinogen levels and platelet counts support the diagnosis. The determination of D-dimer, fibrin(ogen) split products (FSP) and soluble fibrin monomer (FM) further support the diagnosis.Therapeutic approachspecific for DIC, aim to control activation of blood coagulation and bleeding risk.Early diagnosis and prompt treatment backed by laboratory support can reduce the morbidity and mortality associated with it. Despite optimal treatment, DIC carries a very high mortality rate. Because DIC affects many organ systems, most survivors have a prolonged recovery period. [1],[2]

KEYWORDS

DIC, D-dimer

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.

Disseminated intravascular coagulation (DIC) is a life-threatening syndrome characterized by disseminated and often uncontrolled activation of coagulation.It is defined as systemic intravascular triggering of coagulation (resulting in intravascular fibrin clot formation) and concurrent depletion of clotting factors and platelets (increasing the risk of hemorrhage), ultimately resulting in multiple organ dysfunction syndrome (MODS).The signature feature of DIC is the loss of localized activation of coagulation and the inefficiency of natural coagulation inhibitors to downregulate thrombin generation.

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.[3]

DIC may result as a complication of infection, solid cancers, hematological malignancies, obstetric diseases, trauma, aneurysms, and liver diseases, etc., each of which presents characteristic features related to the underlying disorder. (TABLE 1) The risk of DIC is particularly high in patients with sepsis. Indeed, in sepsis DIC occurs in 30% to 50% of them, whereas the frequency of DIC is approximately 10% in patients with solid tumors, trauma, or obstetric calamities. **(TABLE 1)**

Clinical Conditions Triggering DIC	Causes of DIC
Sepsis or severe infection	Potentially any microorganism but particularly gram-negative bacteria Viral infections (i.e. viral hemorrhagic fever) Malaria, Rickettsia infection
Trauma	Severe tissue injury, Head injury, Burns, Fat embolism Surgery, Heat stroke of shock
Organ destruction	Pancreatitis, severe inflammation, tissue necrosis
Malignancy	Solid tumors (pancreatic, stomach, colorectal cancer, mucin secreting adenocarcinoma) Hematological malignancies (acute promyelocytic leukemia)
Obstetrical calamities	Placental abruption, Placenta previa, Amniotic fluid embolism, Intrauterine death Eclampsia, HELLP syndrome
Vascular abnormalities	Aortic aneurysm, Giant hemangiomas (Kasabach-Merritt syndrome), Vasculitis
Liver disease	Cirrhosis Acute hepatic necrosis
Severe toxic or immunological reactions	Graft-versus-host disease, Transplant reaction, Snake bites (such as from those belonging to the genus Echis), Severe transfusion reactions (incompatible blood transfusion reactions)

Three guidelines for diagnosis and treatment of DIC [4–6] have been published in the literature by the British Committee for Standards in Haematology (BCSH), Japanese Society of Thrombosis and Hemostasis (JSTH), and Italian Society for Thrombosis and Haemostasis (SISET). Although these three guidelines are broadly similar, there are variations in several recommendations regarding DIC treatment. Therefore, the subcommittee for DIC of the Scientific and Standardization Committee (SSC)/International Society of Thrombosis and Haemostasis (ISTH) harmonized these three guidelines in a report entitled, Guidance for the diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines.[6] As Early the diagnosis and appropriate treatment of DIC is of critical importance to favourable patient outcomes.

Epidemiology:

Since DIC is a complication of other medical diagnoses, the prevalence of DIC remains greater in higher settings as compare to lower settings. It is a severe or life-threatening diagnosis, associated with the disease.

About 35% of cases of severe sepsis may complicated by DIC. Infection with Gram-negative microorganisms has been associated with DIC; however, the incidence of DIC with Gram-positive infections is similar. Systemic infections with other microorganisms, including fungi or parasites may lead to DIC as well. Factors entangled in the development of DIC due to infections are microbial membrane constituents, such as lipo polysaccharide or lipoteichoic acid, or exotoxins (eg, Staphylococcal α-toxin), evoking a strong immune response and release of cytokines.

Both hematological malignancies and solid tumors may be complicated by DIC due to the expression of pro coagulant factors by

tumor cells. Severe trauma is another clinical condition commonly associated with DIC. In addition, release of tissue material (such as tissue thromboplastin, in particular in patients with head trauma) into the circulation and endothelial disruption may contribute to the systemic activation of coagulation.It may be difficult to differentiate DIC from the coagulopathy due to massive blood loss and the dilutional coagulopathy as a result of massive transfusion or infusion of large volumes of crystalloids that may occur in the first hours after major trauma. In obstetric calamities, such as placental abruption and amniotic fluid emboli, acute and fulminant DIC may occur.

Pathophysiology:

DIC also referred to as consumptive coagulopathy, involves the homeostatic imbalance between coagulation and bleeding. The clinical array includes sepsis, trauma, malignancy, liver disease, obstetric disorders, envenomation, vascular anomalies and major transfusion reactions. The pathogenesis may follow either or both of the pathways mentioned below:

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.

In DIC mechanisms involved in different pathological conditions are:
1. Bacterial septicaemia- which accounts for the major cause of DIC may be due to either cell membrane components of the microorganism or bacterial exotoxins.

2.Severe trauma-release of phospholipids and fat (major fractures) into the circulation can cause haemolysis, endothelial damage and activation of the coagulation cascade.

3.Solid tumours and haematological malignancies- particularly in acute pro-myelocytic leukaemia and some prostatic cancer,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 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.

4.Acute obstetric complications - such as placental abruption, amniotic fluid embolism, rarely pre-eclampsia and intrauterine death of the foetus which alsoleads to DIC,release of thromboplastin-like material in placental abruption is the causative factor which correlates with the degree of separation.

5. Aortic aneurysms and cavernous haemangiomas- may promote DIC by producing vascular stasis or local activation of coagulation system.

6.Snake bites- causes exogenous toxins induced DIC.

Diagnosis:

No single history, physical exam, or laboratory component can lead to a diagnosis of or rule out DIC; therefore, a combination of both subjective, objective, and laboratory findings should be utilized to make a diagnosis of DIC.

Laboratory Test:

Coagulation tests provide important evidence regarding the degree of coagulation factor activation and consumption.[9-10] PT is prolonged in approximately 50% of patients with DIC at some point during their clinical course, abnormalities are also observed in patients with liver disease or vitamin K deficiency.

Reduced platelet count or clear downward trend in subsequent measurements is a sensitive sign of DIC, although this pattern is also observed in patients with bone marrow disorders. A reduced fibrinogen level is a important indicator in a diagnosis of DIC due to leukemia or obstetric diseases; however, it is not observed in most septic DIC patients.

Elevated fibrin-related markers (FRMs), such as FDP, D-dimer, or soluble fibrin (SF), reflect fibrin formation. SF assays offer theoretical advantages in detecting DIC, more closely reflecting the effects of thrombin on fibrinogen, although the half-life is short. It is important to consider that many conditions, such as trauma, recent surgery, bleeding, or venous thromboembolism (VTE), are associated with elevated FRMs.

Reductions in the levels of natural anticoagulants, such as anti thrombin (AT) and protein C, are common in patients with DIC. Although measuring the AT activity is useful for achieving the full efficacy of heparin, this parameter cannot be quickly and easily measured in all hospitals. These activities are correlated with the liver function and/or concentration of albumin.

Elevated soluble thrombomodulin (TM), PAI-I, and von Willebrand factor propeptide levels are often observed in patients with DIC and have been shown to have prognostic significance.

The biphasic waveform of the activated partial thromboplastin time (APTT) has been shown to be associated with DIC and appears to have a positive predictive value for the disease. Although many attractive markers for DIC have been reported, no single marker can be used to diagnose DIC alone. Therefore, four guidelines recommend that DIC could not be diagnosed according to the level of a single marker but rather based on the combination of laboratory markers. Among the four types of DIC, PT, fibrinogen, and platelets are important parameters for diagnosing the massive bleeding type of DIC, while fibrinogen, FDP, and plasmin-plasmin inhibitor complex (PPIC) are important for detecting the bleeding type of DIC. Meanwhile, platelets, PT, and AT are important for diagnosing the organ failure type of DIC and hemostatic molecular markers, such as SF and the thrombin-AT complex, are important for diagnosing the non-symptomatic type of DIC.

Scoring system

In order to facilitate the diagnostic process for detecting DIC, the use of a scoring system is recommended by each of the four different guidelines [4–8]. Three different diagnostic criteria incorporating similar global coagulation tests have been established by the ISTH/SSC , Japanese Ministry Health, Labour and Welfare (JMHLW) , and Japanese Association of Acute Medicine (JAAM). The JMHLW score is well correlated with the severity of DIC and can be used to predict the outcome of the disease. The ISTH overt DIC score is useful and specific for diagnosing DIC due to infective and non-infective aetiologies'. The JAAM score is sensitive for detecting septic DIC and is correlated with the ISTH and JMHLW scores and disease outcome.

The bleeding type of DIC can be easily diagnosed using the ISTH overt-DIC and JMHLW criteria, while the organ failure type of DIC is diagnosed according to the JAAM diagnostic criteria. The massive bleeding (consumptive) type of DIC can be diagnosed using any of the three diagnostic criteria; however, it is difficult to diagnose the non-symptomatic type of DIC using these criteria. The use of hemostatic molecular markers is required to diagnose the non-symptomatic type of DIC.
Differential diagnosis of DIC includes:

1. Massive blood loss
2. Thrombotic micro angiopathy
3. Heparin-induced thrombocytopenia
4. Vitamin K deficiency
5. Liver insufficiency.

Treatment:

The keystone of DIC treatment is providing treatment for the underlying disorders, such as the administration of antibiotics or surgical drainage in patients with infectious diseases and anticancer drugs or surgery in patients with malignant diseases.DIC spontaneously resolves in many cases when the underlying disorder is properly managed and improved. However, some cases require additional supportive treatment specifically aimed at abnormalities in the coagulation system.[9]

Treatment of DIC in four types of DIC:

1.Blood transfusion

Markedly low levels of platelets and coagulation factors, particularly fibrinogen, may increase the risk of bleeding. The above four guidelines recommended the administration of platelet concentrate (PC) and fresh frozen plasma (FFP) in DIC patients with active bleeding or those at high risk of bleeding requiring invasive procedures, without high-quality evidence. The threshold for transfusing platelets depends on the clinical state of the DIC patient. In general, PC is administered in DIC patients with active bleeding and a

platelet count of ≦50×10^9/l. A much lower threshold of 10 to 20×10^9/l is adopted in non-bleeding patients who develop DIC after undergoing chemotherapy. PC may be administered at higher levels in patients perceived to be at high risk of bleeding based on other clinical or laboratory features. The transfusion of PC or FFP is usually performed in patients with the massive bleeding or bleeding types of DIC. It is necessary to use large volumes of plasma in order to correct coagulation defects associated with a prolonged APTT or PT (greater than 1.5 times the normal value) or decreased fibrinogen level (less than 1.5 g/dl).As specific deficiencies in fibrinogen associated with the massive bleeding type of DIC can be corrected with the administration of purified fibrinogen concentrates or cryoprecipitate. The response to blood component therapy should be monitored both clinically and with repeated assessments of the platelet count and coagulation parameters following the administration of these components.

2. Heparin

Although the administration of anticoagulant treatment is a rational approach based on the notion that DIC is characterized by extensive activation of coagulation, there are several differences in the recommendations for the use of heparin in DIC patients between the four guidelines [4–6]. Therapeutic doses of heparin should be considered in cases of DIC in which thrombosis predominates.Patients with DIC are at high risk of VTE events, and the administration of VTE prophylaxis using UFH, LMWH, and/or mechanical methods has become the standard of care in patients with DIC.The administration of heparin is not recommended in patients with bleeding or massive bleeding type of DIC due to the increased risk of bleeding, although it is recommended in those with the non-symptomatic type of DIC in order to prevent the onset of deep vein thrombosis (DVT).

3. Anti-Xa agents

Both Fondaparinux® and Danaparoid sodium® activate AT specifically to inhibit Xa. Treatment with Fondaparinux® is recommended for the prophylaxis of DVT after orthopedic surgery; however, there is little evidence to support its use in critically ill patients and those with other type of DIC. Danaparoid sodium® is used to treat DIC in Japan, although no RCTs have shown any reductions in mortality or the rate of resolution of DIC. There is significant evidence for the use of these drugs as prophylaxis for DVT; however, there is little evidence for the use of these agents in patients with DIC, and they are not recommended in those with the bleeding or massive bleeding type of DIC. These drugs are also not recommended in patients with renal failure.

4. Synthetic protease inhibitors

Synthetic protease inhibitors, such as Gabexatemesilate® and nafamostat®, exhibit multiple-functions that includes antagonistic effects on the kinin/kallikrein system, fibrinolysis, complement system, and coagulation system. As these drugs have mild anticoagulant and antifibrinolytic effects, they are often used in patients with the bleeding, massive bleeding, and non-symptomatic types of DIC.

5. Natural protease inhibitor

The use of agents capable of restoring dysfunctional anticoagulant pathways in patients with DIC has been studied extensively.AT and the heparin/heparinoid complex primarily inhibits Xa and thrombin, while the APC/TM system inhibits thrombin, FVa, and FVIIIa.

6. Antifibrinolytic treatment

Antifibrinolytic agents are effective in treating bleeding, although the use of these drugs in patients with the organ failure or non-symptomatic type of DIC is generally not recommended. An exception may be made in those with the bleeding or major bleeding type of DIC.

CONCLUSION:

Disseminated intravascular coagulation (DIC) is a life-threatening complication of several disease states.DIC is categorized into bleeding, organ failure, massive bleeding, and non-symptomatic types. The diagnosis and treatment of DIC should be carried out in accordance with the type of DIC based on the four guidelines on DIC.No single history, physical exam, or laboratory component can lead to a diagnosis of or rule out DIC; therefore, a combination of both subjective, objective, and laboratory findings should be utilized to make a diagnosis of DIC.

Therapeutic approach specific for DIC, aim to control activation of blood coagulation and bleeding risk. Early diagnosis and prompt treatment backed by laboratory support can reduce the morbidity and mortality associated with it.

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