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Acute Disseminated Intravascular Coagulation

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A 37-year-old man with a 1-week history of chills, fever, and productive cough was brought to the emergency department after he became febrile and disoriented. On examination, he appeared confused and was found to have purpura, epistaxis, and hematuria. Laboratory tests showed a platelet count of 17,000 cells/μL, a white blood cell count of 42,000 cells/μL with a striking shift to the left, a prothrombin time prolonged to 16.5 seconds, an activated partial thromboplastin time prolonged to 63 seconds, a fibrinogen level below 100 mg/dL, and an elevated concentration of fibrin degradation products. A metabolic panel showed kidney injury with a serum creatinine level of 3.1 mg/dL. Peripheral blood smear revealed schistocytes and confirmed thrombocytopenia. A chest radiograph revealed a pleural effusion, which further evaluation revealed to be an empyema. The patient was admitted to the intensive care unit, and surgical consult was obtained for pus drainage and chest tube placement. Cryoprecipitate, platelet concentrate, and fresh frozen plasma were administered to control his bleeding, and broad-spectrum antibiotics were started to treat the infection. His coagulation parameters slowly recovered the next day and the subsequent clinical course was uneventful.

Disseminated intravascular coagulation (DIC) is a clinicopathologic syndrome in which widespread intravascular coagulation is induced by procoagulants that are introduced into or produced in the blood secondary to 1 or more underlying condition(s).[1] With ongoing coagulation, clotting factors, including fibrinogen and platelets, are consumed, and depletion of these factors as well as activation of proteins that promote fibrinolysis may lead to bleeding. Thus, thrombosis and hemorrhage may occur almost at the same time. In addition, microvascular thrombosis due to deposition of fibrin in blood vessels can contribute to multiple organ failure, resulting in increased mortality and morbidity. Management of DIC often is challenging, and no strong evidence shows benefit of any treatments directed at correcting the thrombosis or hemorrhage in DIC.[2–11]

There are 2 clinical forms of DIC: acute and chronic. Acute DIC occurs when a large amount of procoagulant (tissue factor) enters the circulation over a brief period of time, overwhelming the body's ability to replenish coagulation factors and predisposing patients to bleeding. In chronic DIC, smaller amounts of tissue factor are involved, resulting in much less intense stimulation of the coagulation system and allowing the body to compensate for the consumption of coagulation proteins and platelets. This article reviews the evaluation and management of acute DIC.

ETIOLOGY AND PATHOGENESIS

DIC is a complication resulting from various conditions that can lead to activation of coagulation pathways, including infection, trauma, and malignancy (**Table 1**).[2–11] The prevalence of DIC varies among centers due to the wide variety of underlying conditions that may lead to it and lack of uniform diagnostic criteria. DIC occurs in approximately 35% of sepsis cases.[12,13] Gram-negative bacterial sepsis is the most notable infectious cause, but DIC may occur with any cause of sepsis, including viruses and parasites. The course of solid tumors and hematologic malignancies can be complicated by the development of DIC. Expression of tissue factor by cancer cells is thought to play an important role in the pathogenesis of DIC in patients with malignancy.[2–11] Coagulopathy is present in 25% of trauma patients and is associated with a five-fold increase in mortality.[14] Its presence may be confused with coagulopathy secondary to massive blood transfusion. Many other conditions may lead to DIC, but most share as a common feature the expression of tissue factor (FVIIa) by mononuclear or cancer cells or the release of tissue-factor–bearing cells due to tissue injury.

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TAKE HOME POINTS

- Disseminated intravascular coagulation (DIC) is a complex syndrome involving both thrombosis and hemorrhage secondary to an underlying condition.
- Diagnosis relies on recognition of the underlying condition(s) in a patient with clinical manifestations of thrombosis or bleeding (or both) and is confirmed by repeat measurement of coagulation parameters.
- The mainstay of treatment is to correct the underlying condition.
- Blood component replacement therapy may stabilize patients but is reserved for patients with active bleeding.
- Heparin use is controversial, but it may be considered in certain conditions where thrombotic manifestations predominate (eg, purpura fulminans, solid tumors, hemangiomas, dead fetus syndrome).

Table 1. Causes of Disseminated Intravascular Coagulation

Infection	Liver disease
Any microorganisms	Obstructive jaundice
Trauma	Acute hepatic failure
Obstetrical calamities	Prosthetic devices
Amniotic fluid embolism	Autoimmune disease
Placental abruption	Vascular disorder
Retained fetus syndrome	Kasabach-Merritt syndrome
Eclampsia	Large aneurysm
Abortion	Tissue destruction
Malignancy	Severe pancreatitis
Solid tumors	Burns
Myeloproliferative/lymphoproliferative disease	Crush injuries and tissue necrosis
Toxic or immunologic reactions	Rhabdomyolysis
Snake bite	
Recreational drug use	
Transfusion reaction	
Minor hemolysis	
Transplant rejection	

Our understanding of the pathogenesis of DIC is derived from animal studies and studies in humans with sepsis. The 3 major mechanisms underlying DIC are excessive generation and circulation of thrombin, impairment of the natural anticoagulant pathway, and suppression of fibrinolysis. Increased thrombin generation is predominantly mediated by tissue factor, which enters the circulation as a result of tissue damage or enhanced expression of tissue factor on cells in response to endotoxins or cytokines.[2–11] The role of tissue factor in the pathogenesis of DIC has been demonstrated in experimental animal models in which inhibition of tissue factor by a monoclonal antibody suppressed endotoxin-induced thrombin generation.[15]

Despite potent stimulation of the coagulation pathway, it cannot be propagated unless there is a problem with the natural anticoagulation pathways.[16] These pathways include antithrombin III, protein C, and tissue factor pathway inhibitor. Antithrombin is a circulating plasma protease inhibitor that neutralizes mainly thrombin and factor Xa. Plasma levels of antithrombin III, the most important inhibitor of thrombin, are markedly reduced during DIC due to a combination of consumption, degradation by elastase from activated neutrophils, and impaired synthesis.[16,17] Protein C becomes activated when it binds to endothelial surface–associated thrombomodulin. Activated protein C, in association with protein S on phospholipid surfaces, inactivates factors Va and VIIIa. In DIC, protein C is suppressed from a combination of impaired protein synthesis, cytokine-mediated down-regulation of endothelial thrombomodulin, and a decrease in the concentration of the free fraction of protein S, resulting in reduced activation of protein C.[16–18] Tissue factor pathway inhibitor directly inhibits factor Xa, and it complexes with factor Xa to inhibit tissue factor. Its increase in DIC is insufficient in relation to the increase in tissue factor–dependent activation of coagulation.[15,16]

Fibrinolysis is a process in which plasmin, an active form of plasminogen, cleaves fibrin and fibrinogen to restore vessel patency following hemostasis. Activity of plasmin is regulated by vascular endothelial cells that secrete both serine protease plasminogen activators and plasminogen activator inhibitors (PAI-1 and PAI-2). It is suppressed at the time of maximal activation of coagulation due to a sustained rise in plasminogen activator inhibitor-1.[19]

Inflammatory and coagulation pathways interact with each other in DIC, creating a self-perpetuating cycle that leads to further inflammation and coagulation. Activated coagulation proteins stimulate endothelial cells to synthesize pro-inflammatory cytokines, while thrombin and other serine proteases interact with protease-activated receptors on cell surfaces to promote further activation and additional inflammation. Protein C has an anti-inflammatory effect, and the depressed levels of protein C

observed in DIC may aggravate the inflammatory state. Inflammation in turn increases cell destruction, which is a source of more tissue factor that will stimulate an already overactivated coagulation process.[7]

DIAGNOSIS

Clinical manifestations of DIC consist of symptoms and signs of thrombosis or hemorrhage or both. Patients can present with purpura fulminans, multiple organ failure due to microthrombi and the resulting ischemia, and overt, often difficult to control bleeding. The diagnosis of DIC is clinical and is based on recognition of the clinical presentation in the setting of a condition(s) prone to developing DIC and laboratory assessment of several coagulation parameters. It is important to note that no single laboratory test can diagnose DIC with acceptable sensitivity and specificity. The tests commonly used for assessment of DIC are platelet count, fibrinogen level, fibrin degradation product (FDP) assay, D-dimer assay, prothrombin time (PT), and activated partial thromboplastin time (aPTT; **Table 2**). Because DIC is a dynamic process, repeat measurement is necessary.

Thrombocytopenia is the hallmark of DIC, and its presence should prompt consideration of DIC. A low platelet count on initial testing and, in particular, a progressive drop in the platelet count are sensitive signs of DIC and may indicate ongoing thrombin-induced activation and use of platelets.[2,20] However, thrombocytopenia is not specific for DIC as it may be caused by malignancy, liver disease, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and many other hematologic problems. Peripheral blood smear can confirm the presence of thrombocytopenia. Other possible findings on peripheral blood smear may include schistocytes as a result of microangiopathy and large platelets representing an increased population of young platelets as a result of increased platelet turnover and decreased platelet survival.[8,10]

Because thrombin converts soluble fibrinogen to insoluble fibrin during coagulation, the fibrinogen level in DIC would be expected to be low. However, fibrinogen is an acute phase reactant, and patients with conditions that cause elevation in acute phase reactants (eg, inflammation, sepsis) may have normal serum values of fibrinogen. In a consecutive series of patients, the sensitivity of a low fibrinogen level for the diagnosis of DIC was only 28%.[4]

FDP consists of both fibrin and fibrinogen degradation products. Elevated levels of FDP reflect accelerated fibrinolysis due to plasmin and are found in 85% to 100% of patients with DIC.[9] However, FDP is also elevated in various other conditions, including use of oral contraceptives, pulmonary emboli, myocardial infarction, renal disease, and arterial or venous thrombotic or thromboembolic events. Moreover, it may also be negative when measured using the latex agglutination assay when there is only a minimal consumptive process.[9]

Table 2. Laboratory Tests Used in Evaluation of Disseminated Intravascular Coagulation (Descending Order of Reliability)

Profragment 1+2	Protamine test
D-dimer*	Thrombin time
Antithrombin III	Fibrinogen*
Thrombin precursor protein	Prothrombin time*
Fibrinopeptide A	Activated partial thromboplastin time*
Platelet factor IV	
Fibrin degradation product*	Reptilase time
Platelet count*	

*Tests that are used in common practice.

Adapted with permission from Bick RL. Disseminated intravascular coagulation: a review of etiology, pathophysiology, diagnosis, and management: guidelines for care. Clin Appl Throm Hemost 2002;8:18.

D-dimer is formed during fibrinolysis as a result of degradation of cross-linked fibrin by plasmin. D-dimer levels are elevated in almost all cases of DIC, but it may be falsely high in infection, inflammation, pregnancy, and other conditions involving thrombosis. In addition, standardization of the D-dimer assay remains unresolved as there are more than 30 D-dimer immunoassays based on more than 20 different D-dimer–specific antibodies. These assays have been assessed predominantly in venous thromboembolic events, not in DIC, and therefore it is possible for a D-dimer assay to be negative in an obvious case of DIC.[9,21,22]

PT is prolonged in 50% to 75% of DIC cases as coagulation factors are consumed.[8] However, it may be normal in up to 50% of cases due to the presence of circulating activated clotting factors (eg, thrombin or factor Xa), which may accelerate the formation of fibrin, and the presence of early degradation products, which may be rapidly clottable by thrombin.[9] aPTT is prolonged in 50% to 60% of patients with DIC.[9] A normal aPTT cannot be used to rule out DIC because, as with PT, circulating activated clotting factors and early degradation products may lead to a false-positive result. Both PT and aPTT are prolonged when the fibrinogen level falls below 100 mg/dL.[9]

Scoring systems for diagnosing DIC have been developed by the subcommittee on DIC of the International Society of Thrombosis and Haemostasis (ISTH; **Figure**) and by the Japanese Association for Acute Medicine (JAAM; **Table 3**).[23–27] Both systems have been

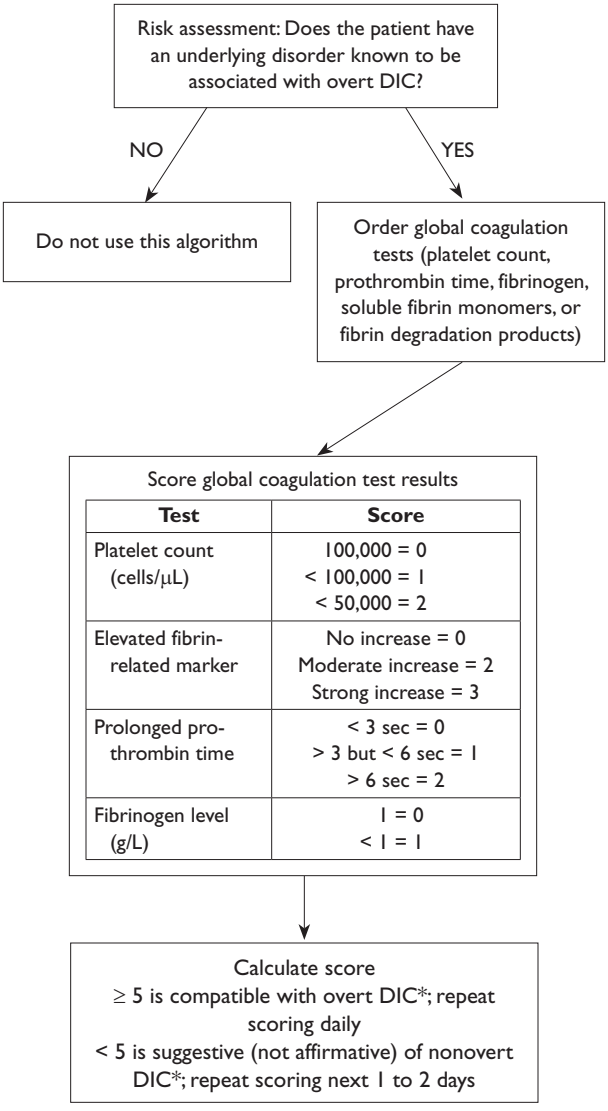

Figure. International Society of Thrombosis and Haemostasis Scoring System for disseminated intravascular coagulation (DIC). *The term overt DIC refers to a decompensated hemostatic system, whereas nonovert DIC refers to a stressed but compensated hemostatic system. (Adapted with permission from Taylor FB Jr, Toh CH, Hoots WK, et al; Scientific Subcommittee on Disseminated Intravascular Coagulation [DIC] of the International Society on Thrombosis and Haemostasis [ISTH]. Towards a definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001;86:1327–30.)

prospectively validated and have a high diagnostic rate; however, the JAAM criteria seem to have an advantage for selection of patients with early DIC.[27]

MANAGEMENT

The main focus of management of DIC is to correct the underlying cause or initiating factor of excessive coagulation. In many instances, correcting the underlying cause may not be possible (eg, cases of malignancy) or may take time. In either event, measures are needed to break the cycle of thrombosis and hemorrhage while treatment of the underlying condition is being pursued. These measures are replacement therapy, which is widely accepted, and the use of anticoagulation, which remains controversial.[9,10]

Replacement of blood components that are deficient due to ongoing consumption is used in selected cases. Specifically, replacement therapy is used only in patients who have clinical symptoms of bleeding and is not used to treat patient with laboratory abnormalities alone.[2–11] Indications and dosage for each blood component are summarized in **Table 4**.[28,29]

Anticoagulant therapy has been suggested as a theoretically rationale approach to address the excessive coagulation seen in DIC.[9] Although anticoagulation may worsen bleeding in these patients, any therapies directed at replacing coagulation factors also may worsen end-organ failure because of worsening thrombosis. Unfortunately, high-quality studies to address this issue have not been conducted. Experimental studies have shown the benefit of heparin in multiple organ failure due to

Table 3. Japanese Association for Acute Medicine Scoring System for Disseminated Intravascular Coagulation

Criteria	Score
Systemic inflammatory response syndrome criteria	
≥ 3	1
0–2	0
Platelet count (cells/μL)	
< 80,000 or > 50% decrease within 24 hr	3
≥ 80,000 and < 120,000 or > 30% decrease within 24 hr	1
≥ 120,000	0
Prothrombin time (patient's value/normal value)	
≥ 1.2	1
< 1.2	0
Fibrin/fibrinogen degradation products (mg/L)	
≥ 25	3
≥ 10 and < 25	1
< 10	0

NOTE: A score of ≥ 4 indicates a diagnosis of disseminated intravascular coagulation.

Adapted with permission from Gando S, Iba T, Eguchi Y et al; Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group. A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. Crit Care Med 2006;34:625–31.

DIC.[30–37] In a murine model of inflammation, mice treated with selectin-blocking antibodies and heparin or a selectin antagonist plus heparin were protected from microvessel obstruction and coagulation, severe vasculitis, respiratory difficulties, and vascular leakage.[31] In mice subjected to injection of *Serratia marcescens* lipopolysaccharide, low-molecular-weight heparin was shown to attenuate multiple organ failure and increase survival compared with placebo.[33] Heparin was also shown to blunt endotoxin-induced activation of coagulation in healthy male human patients, although its significance in the clinical setting is difficult to determine.[32] In summary, there is no strong evidence to support the use of heparin in DIC or that shows a worse outcome in DIC patients who are treated with heparin.[30–37]

Despite this controversy, it is commonly accepted to use heparin in cases where thrombosis seems to predominate (eg, purpura fulminans, solid tumors, hemangiomas, dead fetus syndrome).[2–11] Heparin is usually given at relatively low doses (5–10 units/kg of body weight/hr) by continuous intravenous infusion or subcutaneous injection for long-term outpatient therapy. Low-dose subcutaneous heparin appears to be as effective as or possibly more effective than larger doses of intravenous heparin in DIC.[9,30,36,37] Nevertheless, extreme caution must be exercised when using heparin, and it must be discontinued at the slightest hint of worsening bleeding.

A number of other agents have been studied in DIC treatment, with various results.[11,13,38–46] The use of antithrombin concentrate seems a logical approach, but a large, multicenter randomized trial did not show a benefit.[38] In 1 small study, activated protein C appeared to be more effective than heparin in treating bleeding associated with DIC, but there was little difference in organ dysfunction.[43] A phase III randomized trial of recombinant tissue factor pathway inhibitor showed no mortality benefit as compared with placebo and was linked with increased bleeding risk.[39] Tranexamic acid and aminocaproic acid are rarely used in DIC, but in 1 case report they were reported to control bleeding along with heparin.[41] A phase III trial in Japan showed thrombomodulin to be superior to heparin in improving DIC and alleviating bleeding, suggesting that this compound deserves further investigation.[42] Activated factor VII administered in DIC patients with advanced cancer and associated bleeding that failed to respond to blood product replacement resulted in cessation of bleeding in 15 out of 18 patients.[40] It has also been used successfully to treat bleeding caused by amniotic fluid embolization.[44] Gabexate mesilate (GM) is a synthetic inhibitor of serine proteases (eg, thrombin) that has anticoagulant activity in the absence of antithrombin. A multicenter study in Japan comparing GM and GM with unfractionated heparin showed a greater reduction of the DIC score in the GM arm;[45] however, the clinical significance of this finding is unclear. Finally, hirudin has been evaluated in a pilot study, but no clinical trial has been performed.[46]

Table 4. Blood Component Replacement Therapy

Blood Component	Suggested Dose	Indication
Cryoprecipitate	1 unit/10 kg body weight	Symptomatic bleeding with fibrinogen < 100 mg/dL
Fresh frozen plasma	15–20 mL/kg body weight	Symptomatic bleeding with prolonged PT or aPTT
Platelet concentrates	1–2 units/10 kg body weight	Symptomatic bleeding with platelet count < 50,000 cells/μL *or* < 10,000–20,000 cells/μL without bleeding

Factors Comprising Cryoprecipitate (10–15 mL/unit)

Coagulation Factor	Amount per Unit	Half-life (hr)
Fibrinogen	150–250 mg	100–150
Factor VIII	80–150 units	12
von Willebrand's factor	100–150 units	24
Factor XIII	50–75 units	150–300

Factors Contained in Fresh Frozen Plasma (175–250 mL/unit)

Coagulation Factor	Concentration	Half-life (hr)
Fibrinogen	2–4.5 mg/mL	100–150
Prothrombin (factor II)	~ 1 unit/mL	50–80
Factor V	~ 1 unit/mL	12–24
Factor VII	~ 1 unit/mL	6
Factor VIII	~ 1 unit/mL	12
Factor IX	~ 1 unit/mL	24
Factor X	~ 1 unit/mL	30–60
Factor XI	~ 1 unit/mL	40–80
Factor XIII	~ 1 unit/mL	150–300
von Willebrand's factor	~ 1 unit/mL	24

aPTT = activated partial thromboplastin time; PT = prothrombin time.

CONCLUSION

DIC is a complex syndrome that involves thrombosis and hemorrhage secondary to an underlying condition. Trauma and sepsis are the major causes of DIC. Diagnosis of DIC requires recognition of underlying conditions and repeat measurements of coagulation parameters. Its management is dependent upon early recognition and correction of the underlying condition. Use of blood products is important in managing

bleeding manifestations. Heparin use is controversial but is accepted in certain conditions where the thrombotic process predominates such as purpura fulminans, solid tumors, hemangiomas, and dead fetus syndrome. Other agents have been studied to manage thrombotic or hemorrhagic manifestations of DIC with varying results, and they require further study. **HP**

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