Personal Practice

Disseminated Intravascular Coagulation: Pathophysiology and Principles of Management

R.K. Marwaha
Sudeshna Mitra
Neelam Marwaha*

Disseminated intravascular coagulation (DIC) is a pathophysiologic syndrome wherein specific disease conditions trigger the coagulation cascade. This results in formation of microthrombi in various organs, activation of fibrinolysis and a bleeding tendency. DIC is almost always secondary to specific disorders but occasionally, it may be idiopathic. DIC often accounts for some of the major clinical manifestations of the underlying disease, an example being that of acute promyelocytic leukaemia. It may present either as an acute fulminant condition or as a low grade compensated state. The coagulation disorder may be either localized as in the case of hemolytic uremic syndrome or generalized. In this discussion we shall focus on the pathophysiology and practical aspects of management in acute DIC, which is a medical emergency and often a subject of critical care.

Common Beliefs and Myths

Before discussing the pathophysiology of DIC we shall clarify certain misconceptions commonly held by physicians:

(i) Although septicemia is a common cause of DIC(l), it is not the sole cause. Unless an infectious etiology is very obvious, one should make efforts to exclude other causes by clinical judgement and appropriate investigations.

(ii) The literature highlights the role of *endoxtoxin* released by Gram-negative organisms in the pathogenesis of sepsis induced DIC. However, *mucopolysaccharides* of the bacterial coat of Gram positive organisms can also cause DIC, *e.g.,* staphylococcus(2).

(iii) DIC is widely recognized as a systemic *hemorrhagic syndrome.* However, it is actually a thrombohemorrhagic disorder. Clinicians are watchful of skin bleeds, petechiae or prolonged oozing from venepuncture sites because these are more overt clinical findings. The *microvascular thrombosis* is often clinically silent but it is much more important since it causes multiorgan failure.

(iv) Clinicians equate DIC with fatality. At a stage, when a desperately ill child has shock, bleeding manifestations and evolving organ damage, the treating physician tends to give up hope. However, experience in developed countries has demonstrated that a logical, aggressive and sequential therapeutic approach could significantly reduce morbidity and mortality rates. It is needless to emphasize that such results can only be attained when a good laboratory backup is available round the clock.

*From the Department of Pediatrics and *Hematology, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.*

Reprint requests: Dr. R K. Marwaha, Additional Professor, Department of Pediatrics, PGIMER, Chandigarh 160 012.

(v) Demonstration of fibrinogen degradation products (FDP) has been an essential prerequisite for a diagnosis of DIC. However negative FDPs does not rule out DIC. FDPs are named X,Y,D and E and appear in this sequence. During FDP assay, when thrombin clot tubes are used with the idea of removing fibrinogen, fragments X and Y are also removed. Newer methods which assay D and E have evolved but if secondary fibrinolytic response is minimal then fibrinolysis may stop at X which is not measured. Or else DIC may be formidable and degradation may occur past the stage of D and E. It is also possible that overwhelming release of granulocyte enzymes degrades FDPs.

Causes of DIC and Pathogenesis

DIC has been documented with a number of disease states(l). The ones most commonly encountered in clinical practice are enumerated in *Table I,* alongwith the probable pathogenetic mechanisms operative in the respective disease entity. *Table II* enlists the etiological factors for DIC in pediatric patients in our Institute.

Irrespective of the etiology, DIC is triggered by the activation of either the intrinsic or extrinsic pathway *(Fig. 1).* This occurs in excess of normal so that thrombin is continuously formed and fibrin is deposited inside the vessels leading to ischemia and end-organ damage. Coagulation factors are utilized in the process and platelets are entrapped in the thrombus. As a compensatory mechanism, fibrinolysis is activated. Circulating plasmin cleaves fragments X,Y,D,E from fibrin. These are called fibrin degradation products or FDPs. There is, thus, a precarious interplay of thrombosis versus fibrinolysis. Thrombin is a very potent stimulus for endothelial cells to release tissue plasminogen activator(3). The other major stimulus is kallikrien produced from prekallikrien by activated factor XII.

Owing to accelerated consumption of clotting factors and platelets there is a hemorrhagic tendency. This is compounded by platelet lysis by a plasmin-activated complement system and also by the biodegradation of factors by plasmin, a global protease. The lysis of platelets and some RBCs releases phospholipids which again trigger the coagulation cascade.

Normally fibrin monomers formed from cleavage of fibrin by thrombin, polymerise to form a stable clot. In overwhelming microvascular clot formation, as in DIC, these fibrin monomers combine with FDPs or fibrinogen to form soluble fibrin complexes which again predispose to bleeding. This solubility also acts as a defence against vascular occlusion.

Widespread microvascular thrombosis can result in damage to a number of organs manifesting as: *(a) Brain:* Unexplained coma, focal deficits, occasionally intracranial bleed, delirium; *(b) Lungs:* Adult respiratory distress syndrome, hypoxia, pulmonary edema; (c) *Heart:* Sudden cardiac arrest; *(d) Liver:* Jaundice; *(e) Kidneys:* Oliguria, azotemia, proteinuria, hypertension, and (/) *General:* Peripheral cyanosis, acral gangrene, purpura, features of shock.

In a series of 4906 autopsies done over a 11 year period, 88 cases had microthrombi in > 3 organs and 231 in > 2 organs. The kidney was found to be the most commonly involved organ. In those cases where DIC was suspected but no microthrombi were found, it was hypothesized that either tissue material was far too little or *in vivo* /post morterm lysis of thrombi had occurred or else, the diagnosis was incorrect(4).

TABLE I *Common Causes of DIC and Pathogenetic Mechanisms*

Disease	Probable pathogenesis
Septicemia	
Gram negative and Gram positive fungal, viral infections,	Endotoxin induced - (*i*) release of thromboplastin from monocytes, (*ii*) endothelial sloughing and activation of XII, (*iii*) platelet release reaction
Malignancies	
Acute promyelocytic leukemia Acute myelomonocytic leukemia Solid tumors	Release of thromboplastins from cancer cells and granules of blast forms
Intravascular hemolysis	
Transfusion reactions Paroxysmal nocturnal hemoglobinuria Sickle cell anemia	Release of RBC membrane phospholipids
Vascular malformation	
Giant hemangiomas	Large gaps in endotheium expose subendothelial collagen + release of thromboplastin from poorly supported recurrently injured vessels in the tumor
Snake envenomation	Venoms specifically activate FX or prothrombin, some also contain thromboplastins which produce intravascular hemolysis
Purpura fulminans	
Burns, crush injuries, surgery esp intracranial	Protein C deficiency predisposes to thrombosis in capillaries and venules Release of thromboplastin from damaged tissues
Hypoxic states	
Shock Following cardiac arrest	Acidosis - endothelial sloughing Hypoxia and acidosis stimulate platelet aggregation Hypoperfusion of liver → decreases production of factors by hepatocytes, hypoperfusion of splanchnic bed → decreased reticuloendothelial uptake of activated factors
Acute liver cell failure	Thromboplastin released from liver cell necrosis
Cyanotic congenital heart disease	Role of hypoxia obscure
Collagen vascular diseases and allergic vasculitides	
Polyartritis nodosa, Systemic lupus erythrematosus, Henoch-Schonlein purpura	Probable platelet aggregation and/or factor XII activation by antigen-antibody complexes

It is relatively much easier to suspect DIC when there is some form of abnormal bleeding, *e.g.*, following surgery or some trivial procedure such as venepuncture. Unexplained hematuria or melena may also occur. An average patient of DIC bleeds from at least three unrelated sites(5). One practical problem may arise when

TABLE II–*Etiological Factors of DIC in Pediatric Patients in Our Institute*

Etiological factor	Number of patients	Percentage
Septicemia/Serious infection	38	60.3
Congenital cyanotic heart disease	10	15.8
Post-operative	4	6.3
Hemolytic Uremic Syndrome	4	6.3
Acute renal failure	1	1.5
Acute promyelocytic leukemia	1	1.5
Acute lymphoblastic leukemia	2	3.1
Thalassemia major	2	3.1
Snake bite	1	1.5

bleeding occurs in patients with severe liver disease. In such cases presence/absence of DIC may be difficult to ascertain. Factor VIIIC is increased when liver disease is severe(l). Another similar situation would be to differentiate DIC from septic shock or simple thrombocytopenia both of which may develop independent of DIC in sepsis.

Diagnosis

The minimal requirements for a diganosis of DIC are hemorrhage, thrombosis or both occurring in one of the well-defined clinical situations outlined in *Table I.*

Repeated attempts have been made over the years to define minimal criteria to make a diagnosis of DIC(6). For a definite diagnosis of DIC appropriate laboratory tests must document the presence of: (i) activation of coagulation pathway; *(it)* activation of fibrinolysis; *(Hi)* consumption of inhibitors of the above; and *(iv)* end-organ failure(7). The results and fallacies of the various laboratory tests in DIC are summarized below.

The *(i) prothrombin time (PT)* and *(it) activated -partial thromboplastin (aPTT)* are expected to be prolonged due to consumption of coagulation factors of both extrinsic and intrinsic pathways. However, PT is prolonged in about 75% of patients and aPTT in 50 to 60%. In the rest, PT and aPTT may be normal or even shortened. The reasons for shortening is due to the presence of circulating activated coagulation factors and early degradation products which may be more readily clottable by thrombin. *(Hi) Thrombin time (TT)* is also expected to be prolonged due to hypofibrinogenemia and circulating FDPs which inhibit fibrin polymerisation. However, for reasons mentioned earlier, TT may be normal or shortened. *Coagulation factor assays are not routinely performed and do not provide any further meaningful information, (iv) The platelet count* is typically decreased in DIC. However, the range may be from as low as 2000 to 3000/|al to greater than 100,000/fil. Platelet function is also impaired due to FDP coating of platelet membranes. Platelet function tests, however, add little to the diagnosis, *(v) Paracoagulation tests* - ethanol , gelation or protamine sulfate precipitation detect the presence of circulating soluble fibrin monomer complexes, *i.e.,* complexes of fibrin monomer with early FDPs. Although usually positive, the tests are not specific and may be found in patients with arterial

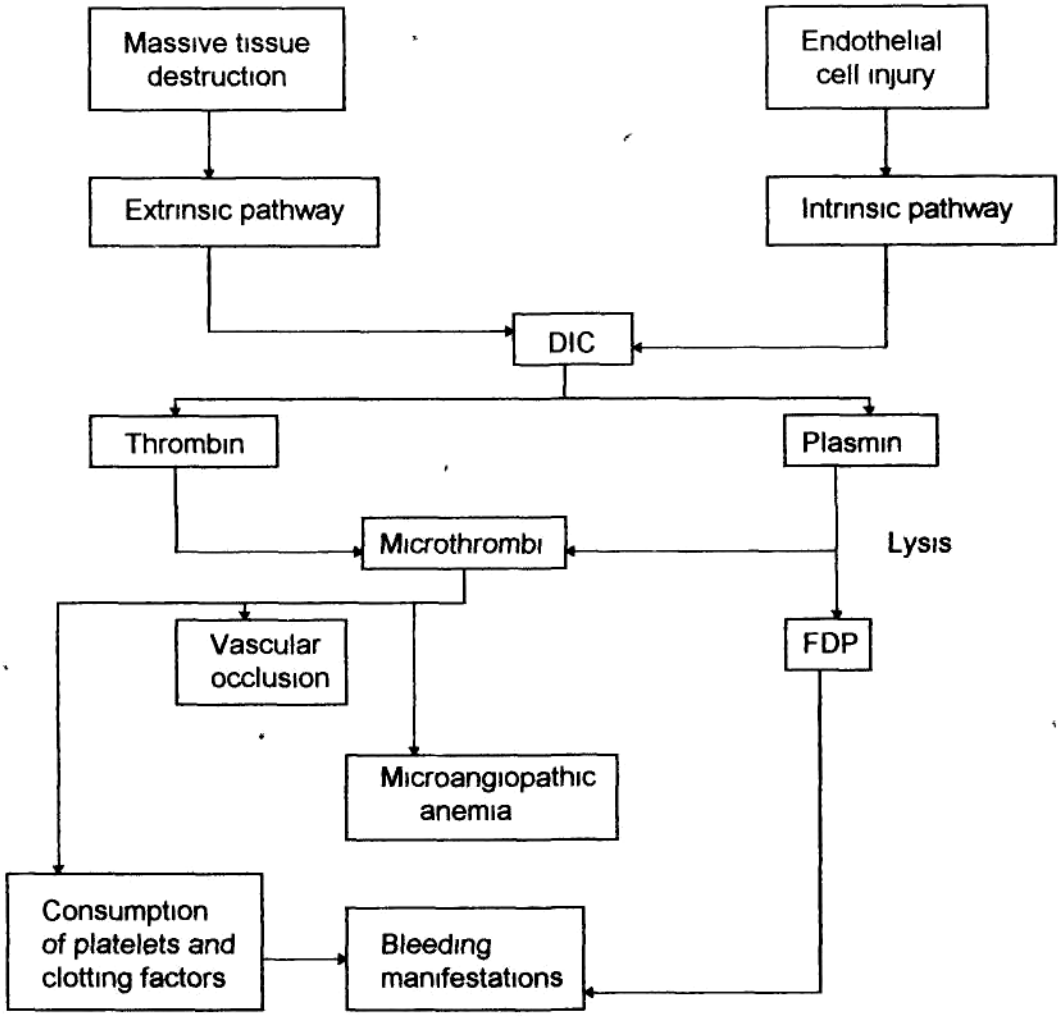

Fig 1 Pathophysiology of DIC

or venous thromboembolism. *(vi) FDPs* are elevated in 85 to 100% of patients with DIC. They indicate plasmin induced biodegradation of fibrinogen/fibrin and, like the soluble fibrin monomer complexes, they can occur in other clinical situations, for example, in patients with thromboembolic events or in certain renal diseases. *(vii) Observing for clot lysis within 10 minutes* has been given much importance but in the presence of hypofibrinogenemia the clot may be friable *per se* and could give a false impression of activated fibrinolysis. Alternatively, the activation of fibrinolytic system may not be enough to give lysis within this time, *(viiiy Peripheral blood film examination:* presence-of schistocytes or fragmented RBCs is seen in only 50% of patients. However, when present, they form an important diagnostic clue in the appropriate clinical situation.

Based on routine laboratory tests, diag-

nostic criteria have been proposed. Considering the fallacies in the above mentioned tests, an attempt has been made to introduce more sensitive and specific tests for diagnosis of DIC. The conversion of prothrombin to thrombin is the key event in initiation of DIC. Thus, tests detecting evidence of thrombin generation have been evolved:

(i) *Prothrombin fragment* (F1+2) - This is released during activation of prothrombin and can be assayed by ELISA or RIA. *(ii) Thrombin-antithrombin* complex (TAT complex) is formed when thrombin combines with its major inhibitor antithrombin. Sensitive immunoassays are available. *(Hi) Reduced antithrombin III levels* - when TAT compexes are formed, the levels of free AT III decrease. Reduced AT III levels have been used in many specialised coagulation laboratories as a key test for diagnosis and monitoring of therapy *(iv) Fibrinopeptide A* levels are increased due to release of the peptide when thrombin converts fibrinogen to fibrin, *(v) Factor Xllla subitnit:* This is decreased as thrombin activates F XIII which cross-links the fibrin monomer, *(vi) D-dimer assay:* FDPs formed after factor Xllla has acted on fibrin. These FDPs are antigenically distinct from fragments X,Y,D, and E, and thus provide evidence of true *fibrin* degradation. D-dimer assay appears to be the most reliable test and ELISA kits for use in clinical laboratories are readily available, *(vii) Proteins C,S and heparin cofactor* II levels are reduced but their estimation is not of much diagnostic help, *(viii)* Reduced *antiplasmin* and *(ix)* elevated *plasmin-antiplasmin* complexes are detected in DIC. The latter appear to have some clinical utility in predicting mortality, especially in trauma-induced DIC.

It is clear from the above that except for a platelet count, screening tests for coagulation and a peripheral blood smear, other tests would not be available in peripheral hospitals. Hence, the management of patients with DIC should ideally be in a center able to provide appropriate laboratory facilities. The minimum laboratory criteria required for a diagnosis of DIC are summarized in *Table 111(8).* The results of laboratory tests in patients (both adults and children), with a clinical suspicion of DIC, seen in our institute are tabulated in *Table IV.*

TABLE III–*Laboratory Criteria for DIC, Based on Routine Laboratory Tests*

Test	Criteria for DIC	
	Adults	Newborns
1 Platelet count (μl)	<150,000	<150,000
2 Fibrinogen (mg/dl)	<150	<150
3 Prothrombin time (%)	<40	<25
4 Activated partial thromboplastin time	>51 seconds	>80 seconds
5 Protamine test/Ethanol gelation	positive	positive
6 Either		
– Thrombin time (more than control)	10 seconds	15 seconds
– Fibrin split products	> 8 μg/ml	>8 μg/ml
Significant fibrinolysis		

Diagnosis is made when at least 3 of the 6 criteria are met with

TABLE IV–*Evaluation of Laboratory Tests in Patients (Adults and Children) with a Clinical Suspicion of DIC.*

Laboratory test	Number of patients with abnormal test	
	Total number	Percentage
Prothrombin time	538/714	75.4
Activated partial thromboplastin time	630/714	88.4
Thrombin time	371/454	81.7
Plasma fibrinogen	150/257	58.4
Platelet Count	567/660	85.9
FDPs (latex agglutination) or fibrin monomers (ethanol* gelation)	362/564	64.2

*Ethanol gelation was found to be a relatively insensitive test in our laboratory.

Management

The principles of management of DIC include an aggressive and logical approach while sustaining hope of recovery from a critical state. Treatment is sequential akin to the therapeutic pyramid followed in some other conditions. Although general guidelines can be stated about stepwise management, every case has to be individualized. Scoring systems have been proposed(6,9) and may be used to grade the severity of DIC. Clinical (hemodynamic) and laboratory parameter monitoring are the cornerstone of successful treatment of DIC. It has been seen that outcome is related to the grade of DIC score when treatment was begun(10).

(a) The first essential step is to *determine the cause of DIC* and *remove the triggering process,* e.g., treatment of septicemia with appropriate antibiotics, management of shock with fluids and inotropes, use of anti-snake venom, surgical removal of giant hemangiomas, *etc.* In one series the alleviation of septic shock appeared to be more important than anticoagulant therapy(11). Anticoagulants are therefore, reserved for those with shock, bleeding or multi-organ failure who have not responded to the first step.

(b) The second step consists of *anticoagulant therapy* to stop intravascular clotting. Heparin is an activator of antithrombin III which can neutralise free thrombin rapidly. The earlier concept was that heparin is indicated when there is evidence of fibrin deposition, *e.g.,* dermal necrosis in purpura fulminans, acral ischemia or venous thromboembolism. The other indications were thought to include retained dead fetus with hypofibrinogenemia, excessive bleeding in giant hemangioma and neoplastic disease(12). However, the current thinking is that after an arbitrary period of 4-6 hours of starting step 1, anticoagulation should be started, if there is no response(9). The only contraindications are DIC related to CNS injury, liver failure or obstetric accidents. The options of heparin administration are high dose (70-140 U/kg) intravenously every 4-6 hours or low dose (80-100 U/kg) every 4-6 hours subcutaneously. The latter has no risk of hemorrhage in contrast to the former. Dermatan sulphate has been tried as an alternative to heparin in acute leukemics with DIC and has been found to be as effective as heparin(13). Another anticoagulant which has been used is antithrombin(AT) III. AT III levels fall in DIC and heparin may become ineffective in such a case. Also, heparin - AT III complex-

es inhibit activated coagulation at a faster rate than AT III alone. So prior small infusion of heparin followed by transfusion of AT III has been tried successfully(14). Other drugs that have been tried are recombinant hirudin, defibrotide and gabexate. About 75% patients respond to steps 1 and 2(5). Coumarin anticoagulants are ineffective in DIC(l).

The routinely available coagulation parameters do not have any value while monitoring patients on anticoagulants owing to their non-reliability as already mentioned. Effectiveness of therapy can be judged by *(i)* clinical improvement, and (n) fall in FDP level, rise in fibrinogen level and normalisation of AT III level.

(c) If patients continue to bleed after the above modalities of treatment, one should suspect component depletion. *Component replacement* should be done cautiously avoiding fibrinogen containing blood products since this will amount to adding fuel to the fire. In the presence of fibrinogen there will be more FDPs which will form soluble complexes with fibrin monomers resulting in hemorrhage. Where DIC is still active as estimated by laboratory methods, washed RBCs, platelets, volume expanders and AT III are safely administered. If these parameters are improving, any component may be used(9).

(d) Rarely, cases require a fourth step that is *inhibition of fibrinolysis*. One such situation is acute promyelocytic leukemia where primarily there is activation of fibrinolysis and another is unexplained ongoing secondary fibrinoloysis. Heparin may help in preventing DIC occurring acutely after chemotherapy. But if α_2-antiplasmin levels are low, epsilon-amino-caproic-acid (EACA) should be added(15). The hazard of antifibrinolytic therapy is that continuously forming microthrombi will not be lysed. Hence it is important to take this step only after proper trial of the first three. Preconditions for such treatment are demonstration of circulating plasmin and cessation of clotting. Drugs used in this category include EACA and tranexamic acid, the latter being more safe. Both are administered intravenously.

Summary

DIC is a thrombohemorrhagic syndrome which occurs in association with well-defined clinical disorders such as septicemia, acute leukemia, snake envenomation, hypoxic states, *etc.* These disease conditions trigger the coagulation cascade *in vivo* resulting in formation of microthrombi, activation of fibrinolysis and a bleeding tendency. The important and most frequently observed laboratory abberrations include reduced platelet counts, low levels of fibrinogen, factors V and XIII with increased FDP's. Therapy primarily consists of recognizing the cause of DIC, removing the triggering process and administering anticoagulant therapy in specific situations. Component replacement is required if patients continue to bleed inspite of instituting the above mentioned measures. Rarely, drugs which inhibit fibrinolysis may be indicated. Early recognition and prompt institution of appropriate remedial measures coupled with adequate laboratory monitoring help in reducing morbidity and mortality due to DIC.

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