DISSEMINATED INTRAVASCULAR COAGULATION

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Disseminated intravascular coagulation (DIC) is also termed as defebrination syndrome or consumptive coagulopathy .

This syndrome is characterized by a hemorrhagic diathesis with unrestrained clotting and fibrinolysis in the vascular microcirculation, initiated by activation of the intrinsic or the extrinsic system, or both.

There is excessive deposition of fibrin throughout the vascular tree, with simultaneous depression of the normal coagulation inhibitory mechanisms. It is triggered by the appearance of procoagulant material (tissue factor-TF or equivalent) in the circulation in amounts sufficient to overwhelm the mechanisms that normally restrain and localize clot formation. This may be the result of either extensive endothelial injury, which exposes TF of fibroblastic origin or the release of TF into the circulation as occurs with amniotic fluid embolus, extensive soft tissue damage, severe head injury or any cause of a systemic inflammatory response.

Release of tissue thromboplastin from injured tissue or from leukocytes activates the extrinsic system. Whereas damage to vascular endothelium (in addition to releasing tissue thromboplastin) results in activation of the intrinsic system via collagen exposure. Exposed collagen initiates platelet aggregation with release of platelet factor III and also activates factor XII directly. The net result is deposition of fibrin in the microvasculature.

This results in a microangiopathic hemolytic anemia with fragmentation of red blood cells as they traverse these vascular beds. These fragmented red blood cells,or schistocytes, seen on the peripheral blood smear are a classic finding in this syndrome. Additionally, microthrombi cause stasis and ischemia in a number of capillary beds, manifesting as renal insufficiency or failure with kidney involvement, pulmonary insufficiency with lung involvement, mental status changes with brain involvement, or dermal necrosis with skin involvement. Thus, the microvascular occlusion by fibrin causes tissue ischemia, contributing to multiorgan failure. Stasis itself can result in further activation of clotting factors.

Fibrin deposition and endothelial wall damage both bring about the release of plasminogen activator, which catalyzes the conversion of circulating plasminogen to plasmin. Plasmin proteolytically hydrolyzes both fibrinogen and fibrin (secondary fibrinolysis), resulting in fibrinogen and fibrin degradation products (FDP). FDPs then interfere with fibrin polymerization through the formation of complexes, further contributing to the hemorrhagic state. FDPs also interfere with platelet function, impairing both adhesion and aggregation.

In the post-operative and ICU patients, infection is the principle cause for DIC. The causative organisms are Gram-negative bacteria, such as the Enterobacteriaceae as well as the nonlactose fermenters; Gram-positive bacteria; rickettcial organisms (Rocky Mountain spotted fever); mycotic infections, such as disseminated aspergillosis; parasitic agents, such as malaria; and viruses. In Gram-negative infections, the endotoxins (cell wall lipopolysaccharide) trigger the intrinsic system by activation of factor XII directly and by exposing factor XII to subendothelial collagen, as a result of endotoxin-mediated damage to vascular endothelium. Endotoxins may also trigger the coagulation cascade by inducing procoagulant activity in circulating leukocytes, hepatic macrophages, and endothelial cells.

Endotoxins activate the extrinsic system by the release of tissue thromboplastin from damaged leukocytes and vascular endothelium.

Traumatic injuries (particularly involving brain, bone, or liver), thermal injuries, and severe crush injuries, as well as surgical procedures may produce a consumptive coagulopathy. Secondary infections and hemorrhagic shock further aggravate the coagulopathy, especially if there is acidosis, hypothermia, or tissue ischemia and necrosis.

Acut pancreatitis, arising from various causes, may be associated with DIC due to release of enzymes that may directly activate a number of coagulation factors. In many instances, there is associated multiorgan dysfunction. The pyogenic sequelae, such as the infected pancreatic necrosis or abscess formation, may result in DIC attributable to sepsis.

Obstetric complications can result in some of the most profound and challenging instances of DIC. Well-recognized examples include amniotic fluid embolism, abruptio placentae, retained dead fetus, and eclampsia. In these circumstances, the culprit is massive systemic release of tissue thromboplastin that generates a fulminant course characterized by bilateral renal cortical necrosis to frank cardiopulmonary collapse, shock, multiorgan failure and at times death, even if aggressive attempts are made to treat these individuals.

The diagnosis of DIC.

The clinical manifestations of DIC are a consequence of both thrombosis and bleeding. Bleeding is a more common clinical presentation in patients with acute, fulminant DIC. Petechiae, ecchymoses, epistaxis, gingival/mucosal bleeding, hematuria, and bleeding from wounds and puncture sites may be evident. With the chronic forms of DIC, thrombotic manifestations are more likely. Organs with the greatest blood flow, for example, kidney and brain, typically sustain the greatest damage. Pulmonary function may deteriorate as a consequence microthrombus accumulation.

The PT, PTT, and TT are all prolonged. PT and aPTT may remain normal in spite of decreasing factor levels because of the presence of high levels of activated factors including thrombin and Xa.

The platelet count is decreased. Thrombocytopenia (<10000/uL) is not always evident early in the process, but true DIC without sequential reduction in platelet count is very unlikely.

Fibrinogen level may not be decreased initially (<100 mg/dL), particularly in the presence of adequate hepatic function. Fibrinogen is an "acute phase reactant," which increases in response to stress and the early consumption of fibrinogen may simply reduce its levels to "normal."

Fibrin degradation products are elevated. FDPs are a sensitive measure of fibrinolytic activity although they are not specific for DIC. D-dimer (which is a breakdown product of the crosslinked fibrin in a mature clot) is somewhat more specific for DIC, but not entirely so, and should be measured when DIC is suspected.

The peripheral blood smear often reveals the presence of schistocytes.

Factors I (fibrinogen), V, VIII, and XIII tend to be markedly depressed. Factor VIII is decreased in DIC but normal with hepatic failure without DIC.

Levels of prothrombin fragments F1+F2 (a marker of prothrombin conversion to thrombin-increased), thrombin-ATIII complexes (increased), ATIII (decreased), alpha-2 antiplasmin (decreased by binding to excess plasmin), protein C (decreased), plasminogen (decreased).

Radioimmunoassays of fibrinopeptide A, a by-product of the action of thrombin on fibrinogen may be useful in these situations to establish the correct diagnosis.

Although rare, primary fibrinolysis differs from DIC (where secondary fibrinolysis occurs) in the following ways. In primary fibrinolysis (a) platelet count is normal (b) soluble fibrin monorners are not present (measured by the plasma paracoagulation test) (c) schistocytes (red cell fragments) are not seen and (d) tests for increased levels of plasmin activity are strongly positive (euglobulin clot lysis time, whole blood clot lysis time).

Management of DIC.

The number of disorders associated with DIC is substantial, but the unifying approach to management is supportive therapy with replacement of coagulation factors and platelets with attention focused on treating the underlying disease process. Septicemia will require antibiotic therapy and surgical debridement and drainage for control of infectious complications. The obstetric conditions are frequently self-limited, although evacuation of the uterus or hysterectomy may be warranted. Hypovolemia, acidosis, and hypoxemia should be corrected to prevent their contribution to the DIC process. When bleeding becomes life threatening, the consumptive coagulopathy must be treated. Platelets will be required for thrombocytopenia, for example, <50,000/mm3. FFP will replace the clotting factor deficiencies. Fibrinogen level should be raised to >100 mg/dL. When hypofibrinogenemia is severe (<50 mg/dL) cryoprecipitate is required. Six units of cryoprecipitate will increase fibrinogen level by approximately 50 mg/dL in a 70-kg patient.

The end point is normalization of the PT, PTT, TT and platelet count.

FFP and platelet concentrates are the two most common blood products used as a temporizing measure. Stored or banked whole blood is a reasonable source of most clotting factors if the units are less than 21 hours old. The biologic half-life of factors V, VII, VIII, and IX are on the order of 24 hours or less; hence whole blood stored for longer than 24 hours may not provide adequate amounts of these coagulation factors.

Heparin has been advocated. However, the contemporary practice is to restrict its use to only those situations where thrombosis is clinically problematic, principally DIC associated with malignancies. There is no proven benefit in situations in which bleeding is the predominant manifestation. Antifibrinolytics have been considered. However, their use in the face of widespread thrombosis is potentially disastrous and they should not be used. Antithrombin III concentrates have been administered. The hope is that its administration will serve to slow the runaway coagulation process.
In septic patients with or without DIC, treatment with recombinant activated protein C reduces mortality and this may be attributable in part to its profibrinolytic, anti-inflammatory and anticoagulant effects.