REVIEW

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Disseminated intravascular coagulation: Treat the cause, not the lab values

ABSTRACT

Disseminated intravascular coagulation (DIC) is a manifestation of an underlying pathologic process such as cancer, infection, trauma, or obstetric catastrophe. It can manifest as thrombosis, bleeding, or both. To succeed, treatment must address the underlying cause.

KEY POINTS

No single laboratory test is sensitive or specific enough to definitively diagnose DIC. Rather, laboratory tests serve to confirm one's clinical suspicion.

The clinical manifestations or laboratory abnormalities of several conditions may mimic or be indistinguishable from those in DIC, and it is important to differentiate these conditions from acute DIC.

It is important to recognize the underlying process of DIC and to direct effective therapy toward that cause. Replacement of consumed blood products alone will not be effective.

Blood product replacement with platelets, cryoprecipitate, or fresh frozen plasma is typically indicated only in patients with active bleeding or at high risk for bleeding, not those with laboratory abnormalities alone.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC) is always secondary to an underlying disorder (eg, trauma, cancer, infection, or obstetric catastrophe) that is usually obvious.

A common and serious error in managing DIC is to waste time trying to correct abnormal laboratory values by giving blood product infusions, thus delaying needed treatment of the underlying condition. Therapy directed at the laboratory manifestations of DIC may, at best, stabilize the patient but not change the course of the underlying disorder.

In this article we examine how DIC arises, its clinical manifestations, its diagnosis, and its treatment.

WHAT IS DIC?

DIC is a complication of an underlying derangement, disease, or pathologic process that results in excessive stimulation and activation of the coagulation system. The result is thrombotic microangiopathy and secondary fibrinolysis.

DIC has also been termed consumption coagulopathy, defibrination syndrome, and consumptive thrombohemorrhagic disorder. While such terms are accurate in their description, "DIC" appears to be the universally accepted term.

In DIC, continuous stimulation of hemostasis gives rise to overwhelming and unregulated activation of the hemostatic system with pathologic circulation of thrombin and plasmin, which explains the patient's physical and laboratory findings. Clinical manifestations of DIC may include either thrombosis, hemorrhage, or both. Successful therapy hinges on

gaining control of the underlying stimulus of coagulation.

HEMOSTASIS IS A BALANCE OF FORCES

Physiologic hemostasis is tightly controlled as a balance of forces promoting and impeding coagulation and fibrinolysis.

Forces promoting coagulation

In response to injury, coagulation may be initiated via either the intrinsic or the extrinsic pathway.

The intrinsic pathway constantly generates thrombin in small amounts, resulting in a slow, natural turnover of fibrinogen.[1] After an injury, the intrinsic pathway may be further activated when blood is exposed to subendothelial tissue and collagen due to disruption of the endothelial lining of the blood vessels.

The extrinsic pathway is activated by exposure of blood to tissue-factor-bearing cells as a result of tissue disruption or induction of tissue factor expression on cells such as endothelial cells or monocytes and macrophages.

Clinical manifestations of DIC include thrombosis or hemorrhage, or both

Thrombin is a final common product of both the intrinsic and extrinsic clotting systems, although the predominant force in hemostatic response to injury appears to be the extrinsic (tissue-factor-driven) system.[2] Thrombin generation induces platelet aggregation and acts to convert soluble fibrinogen to insoluble fibrin, both of which form a hemostatic plug at the site of local injury.

Forces impeding coagulation

Several antithrombotic pathways precisely regulate the physiologic response to injury and limit harmful extension of the hemostatic plug. Antithrombin III, thrombomodulin, protein C, protein S, tissue factor pathway inhibitor, and the reticuloendothelial system limit thrombin generation by neutralizing any circulating activated products of coagulation. Hence, control of initiated coagulation relies on the integrity of these control pathways.

Forces promoting fibrinolysis

Fibrinolysis is also an important part of the normal hemostatic balance as components of the fibrinolytic system are incorporated into

the developing fibrin clot.

Clot lysis begins immediately after the clot is formed. Tissue plasminogen activator is released from endothelial cells and initiates local fibrinolysis by activating plasminogen adsorbed onto fibrin clots.

Circulating thrombin is rapidly complexed to and neutralized by thrombomodulin bound to the endothelial cell membrane. The thrombin-thrombomodulin complex serves to activate protein C. Plasmin, generated from plasminogen with the assistance of activated protein C, acts to degrade fibrin, with resultant generation of fibrin degradation products.

Forces impeding fibrinolysis

The reaction of plasmin remains localized under normal conditions, as inhibitors of both plasmin and tissue plasminogen activator exist. The inhibitor of plasmin, alpha-2-plasmin inhibitor (alpha-2-PI), rapidly neutralizes any excess plasmin that escapes the clot before it enters the circulation. Plasminogen activator inhibitor-1 (PAI-1) is released from endothelial cells, blocking further activation of tissue plasminogen activator.

Any perturbation, either congenital or acquired, of any of these components may allow coagulation to proceed unrestrained by physiologic control.

HOW DIC DEVELOPS

DIC is due to excessive activation of coagulation.

Unregulated activation of the hemostatic system results in the clinical syndrome known as DIC. Excessive activation of coagulation, coupled with the inability to neutralize circulating activated procoagulants as physiologic inhibitors are overwhelmed, distinguishes DIC from physiologic clotting.

Potent thrombogenic stimuli cause uncontrolled, continued, and excessive generation of circulating thrombin. The consequence is pathologic fibrin deposition throughout the microvasculature.

Microvascular thrombosis causes tissue ischemia, contributing to the development of multiorgan dysfunction syndrome. Circulating red blood cells are sheared by the mechanical stress caused by intravascular fibrin strands. As a consequence, microangiopathic hemolytic anemia develops (FIGURE 1).

Microangiopathic hemolytic anemia secondary to sepsis-induced DIC

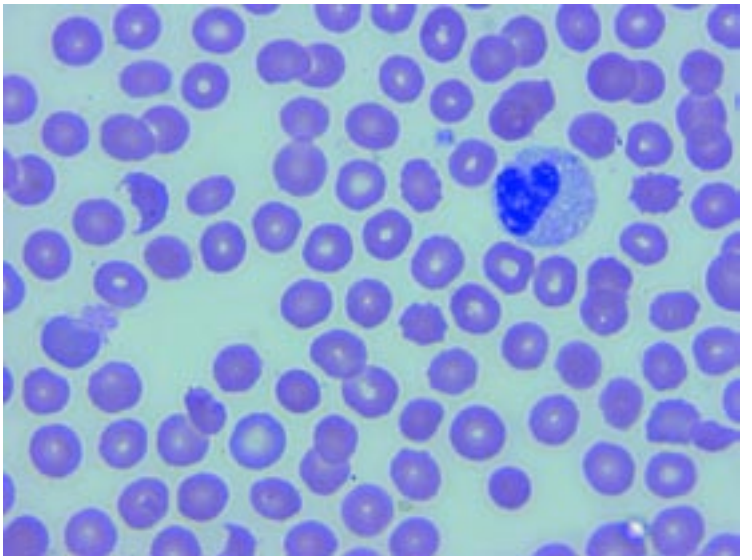

FIGURE 1. Peripheral blood smear from a patient with microangiopathic hemolytic anemia secondary to sepsis-induced DIC. Fragmented red blood cells (schistocytes) are present, platelet number is reduced, and vacuoles and robin-egg blue Doehle bodies are visible within leukocytes. (Wright-Giemsa stain; × 1,000).

Excess thrombin and subsequent widespread deposition of fibrin enhance platelet aggregation in nonphysiologic areas and consumption of coagulation factors. In addition, excessive circulating plasmin produced in response to widespread intravascular microthrombi acts to degrade fibrinogen, fibrin, and other coagulation factors. The consumption of these factors, as well as fibrinolysis, enhances hemorrhage.

Inhibitors of coagulation are overwhelmed

Natural inhibitors of thrombin and plasmin are overwhelmed by continuous activation of coagulation. When these inhibitors are exhausted, thrombin and plasmin are free to circulate unbound and mediate the clinical syndrome of DIC.

At the end of the procoagulant pathway, activated factor XIII stabilizes fibrin clots by forming cross-links between adjacent alpha and gamma chains of fibrin. During fibrinolysis, these cross-links are lysed by plasmin and

TABLE 1

Causes of disseminated intravascular coagulation (DIC)

Sepsis
- Bacterial
- Viral
- Parasitic
- Rickettsial
- Fungal

Severe trauma
- Central nervous system injury
- Crush injury
- Burns
- Frostbite
- Fat embolism

Malignancy
- Solid tumors, especially metastatic adenocarcinoma
- Hematologic malignancy
- Chemotherapy
- Trousseau syndrome
- Tumor lysis syndrome

Obstetric conditions
- Amniotic fluid embolism
- Abruptio placentae
- Placenta previa
- Retained dead fetus syndrome
- Therapeutic abortion
- Toxemia of pregnancy/eclampsia/HELLP* syndrome
- Uterine atony
- Bilateral renal cortical necrosis of pregnancy

Vascular malformation
- Abdominal aortic aneurysm
- Giant hemangioma (Kasabach-Merritt syndrome)

Toxins
- Snake bites
- Amphetamine overdose

Immune-mediated disorders
- Severe allergic reaction
- Acute transplant rejection
- Hemolytic transfusion reaction

Miscellaneous
- Shock
- Cardiac arrest
- Near-drowning
- Heat stroke

*Hemolysis, elevated liver function tests, low platelets

a specific fibrin degradation product termed D-dimer is generated.

An immunoassay for D-dimer specifically measures cross-linked fibrin derivatives. Thus, in DIC, the prior existence of thrombin and plasmin together in the circulation is verified by the presence of D-dimer complex.[3]

CAUSES OF DIC

A variety of clinical conditions can induce DIC, including infection, severe trauma, malignancy, and obstetric catastrophes, all of which are characterized by tissue destruction and subsequent release of tissue factor and other cytokines (TABLE 1).

Infection

Infection is a common cause of acute, severe DIC.[4] DIC can be caused by nearly any type of microorganism. Components of these microorganisms activate cytokines (chiefly tumor necrosis factor and interleukin-6), inducing an inflammatory response and triggering coagulation.

Anything that enhances the spread of the infection (immunosuppression, hepatic insufficiency, or functional or anatomical asplenia[5]) can foster the development of DIC.

Sepsis-associated DIC is particularly instrumental in infarctive necrosis of the microcirculation of the skin, ie, purpura fulminans.[6]

Severe trauma

Severe trauma, particularly involving brain tissue, is associated with DIC. In fact, closed head injury serves as a model for acute, severe DIC.[7] The release of tissue factor from damaged tissue into the systemic circulation leads to coagulation activation. The severity of head injury and ensuing hemostatic system defects are predictors of adverse clinical outcome.[7]

The DIC seen in trauma is greatly promulgated by concurrent shock. With impaired perfusion of the reticuloendotheial system, activated coagulation factors can accumulate in the blood, further enhancing DIC.

Malignancy

Solid tumors (particularly metastatic adenocarcinomas) and hematologic malignancies may be complicated by DIC. Tissue factor expressed on the surface of tumor cells has been implicated in the development of DIC.[8]

Slow, ongoing tumor-initiated DIC is often more thrombotic than hemorrhagic in presentation, with the sine qua non being Trousseau syndrome (chronic compensated DIC, closely associated with adenocarcinoma). On the other hand, DIC in cancer may present as brisk hemorrhage, especially following rapid cell death after effective therapy resulting in tumor lysis syndrome.

On initial presentation or when starting cytotoxic chemotherapy, many patients with acute promyelocytic leukemia experience a severe hyperfibrinolytic state in addition to massive activation of coagulation. All-*trans*-retinoic acid induces tumor cell differentiation and ameliorates severe DIC associated with acute promyelocytic leukemia.[9]

Obstetric catastrophes

Several obstetric complications can result in DIC. Amniotic fluid embolism, placenta previa, and abruptio placentae can cause acute activation of the coagulation cascade; brisk DIC is seen in more than 50% of patients with these conditions.[10] Tissue factor from a retained dead fetus or abruptio placentae gradually enters the maternal systemic circulation and initiates DIC.

Although DIC can be explosive in these patients, it can be short-lived if the obstetric catastrophe is corrected, as the patients are generally otherwise healthy and the intact reticulo-endothelial system rapidly clears the circulation of activated products of coagulation.

A PRACTICAL APPROACH

A practical approach to categorize and understand the many clinical presentations of DIC is by its progression (acute or chronic), extent (localized or systemic), and chief manifestation (thrombotic or hemorrhagic).

Acute or chronic?

DIC can be distinguished as either acute or chronic, depending on the rapidity in which the initiating event is propagated and promulgated. Classic causes of acute DIC include bacterial sepsis or massive trauma, whereas chronic DIC is caused by retained dead fetus syndrome, large abdominal aortic aneurysm, or Trousseau syndrome.

TABLE 2

Clinical findings in disseminated intravascular coagulation (DIC)

Hemorrhage
- Extensive skin and mucous membrane bleeding
- Hemorrhage from surgical incisions, wound sites, catheter or venipuncture sites

Thrombosis
- Purpura fulminans
- Peripheral acrocyanosis
- Pregangrenous changes in digits, genitalia and nose

Localized or systemic?

The extent of DIC can be classified as localized or systemic. Examples of localized causes of DIC are abdominal aortic aneurysm and obstetrical complications such as abruptio placentae. Severe infections with sepsis or burns are models for systemic causes.

Thrombotic, hemorrhagic, or both?

Further characterization of DIC is based on clinical manifestation. DIC can cause thrombosis, hemorrhage, or occasionally both. Trousseau syndrome is an example of thrombotic DIC; hemolytic transfusion reaction (as seen in ABO blood group incompatibility) is an example of hemorrhagic DIC.

In DIC, laboratory tests serve to confirm one's clinical suspicion

DIC IS A CLINICAL DIAGNOSIS

The diagnosis of DIC is clinical.[11] It is made in the context of the patient's history with astute recognition of a constellation of factors, including the clinical presentation supported by perturbations in selected laboratory data.

Clinical manifestations

Clinical manifestations of DIC are bleeding and thrombosis, (TABLE 2) alone or in combination, with ensuing and perhaps progressive organ dysfunction.

Bleeding is typically acute and from multiple sites. Intravenous and intra-arterial line sites, previously dry for days, may begin to ooze. Epistaxis and gum bleeding are common as are petechiae and purpura, which can

progress to purpura fulminans, especially in cases due to septicemia. Blood, hemoglobin, or both may appear in the urine and, along with shock, may be the only indication of intraoperative DIC. Hemodynamic instability and metabolic derangements are frequently observed in patients with acute severe DIC, often occurring secondary to the inciting process.

No single test is diagnostic of DIC

No single laboratory test is sensitive or specific enough to definitively diagnose DIC. Rather, laboratory tests serve to confirm one's clinical suspicion.

A combination of simple and readily available laboratory tests confirms the clinical diagnosis of DIC; these tests include the platelet count, prothrombin time, activated partial thromboplastin time, thrombin time, fibrin degradation product assay, D-dimer assay, and peripheral blood smear. Should these tests be normal, a cause other than DIC should be sought to explain the patient's situation.

Platelet count. Moderate thrombocytopenia is characteristic of DIC and is very sensitive, but not specific.

A moderately low platelet count is very sensitive for DIC, but not specific

Clotting times. As coagulation factors are consumed in DIC, the prothrombin time and activated partial thromboplastin time are prolonged in 50% to 75% of clinically severe cases.[11] They usually do not correct when the patient's plasma is mixed 1:1 with normal plasma, owing to the inhibitory properties of the circulating fibrin degradation products.

Fibrinogen concentration. In 70% to 80% of cases, the thrombin time is markedly prolonged, owing to low levels of fibrinogen and high levels of fibrin degradation products.[11] Reduced plasma fibrinogen levels may be seen in DIC. Some report that severely low plasma fibrinogen levels (≤ 50 mg/dL) are associated with more bleeding in DIC. Although measurement of plasma fibrinogen concentration is widely available, alone it is an unreliable measurement of DIC.

Fibrinogen is an acute-phase reactant, and its concentration may be high before DIC develops, owing to the previously existing process (eg, pregnancy, cancer, or inflammation). Therefore, although DIC causes it to fall, the fibrinogen level may appear normal at first glance.

Fibrin degradation products, D-dimer. Detection of fibrin degradation products confirms accelerated fibrinolysis due to plasmin. The test is highly sensitive, as abnormal fibrin degradation products are found in 95% of cases of DIC.

Elevated D-dimer measurements reflect cross-linked fibrin degradation and are suggestive of DIC.[3] The finding of concurrent elevation of both fibrin degradation products and D-dimer in a patient clinically suspected of having DIC is nearly 100% specific for DIC.[3]

The blood smear may demonstrate fragmented red blood cells (schistocytes) in about half of DIC cases. The degree of microangiopathy is typically less than that seen in thrombotic thrombocytopenic purpura. Review of the blood smear can also confirm thrombocytopenia. Patients with sepsis typically have vacuolization of the polymorphonuclear leukocytes (FIGURE 1).

Laboratory findings are of secondary importance in the diagnosis and management of DIC. Laboratory evaluation of DIC is difficult and the results may be confusing, as DIC is a very dynamic process. Laboratory values can change rapidly with the patient's clinical situation. Although more elaborate laboratory evaluations of DIC have been described, they are typically not practical because they are expensive and not readily available.

DIFFERENTIAL DIAGNOSIS OF DIC

The clinical manifestations or laboratory abnormalities of several conditions may mimic or be indistinguishable from those in DIC, and it is important to differentiate these conditions from acute DIC. Four of the more common conditions are:

- Thrombotic thrombocytopenic purpura
- Chronic DIC (Trousseau syndrome)
- Fulminant hepatic failure
- HELLP syndrome (hemolysis, elevated liver function tests, and low platelets).

Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura clinically resembles DIC, but its pathogenesis and

TABLE 3

Manifestations of organ dysfunction as a consequence of DIC

Perturbation in serum markers of liver, renal, and cardiac function
Jaundice
Oliguria
Cardiac rhythm disturbances
Diffuse alveolar hemorrhage
Adult respiratory distress syndrome
Central nervous system abnormalities
Gastrointestinal mucosal ulcerations
Adrenal insufficiency
Petechiae and purpura fulminans

The onset of multiple organ dysfunction is ominous

treatment are different. Patients present with organ dysfunction, thrombocytopenia, and microangiopathic hemolysis. Petechiae and purpura are rare. A normal prothrombin time, activated partial thromboplastin time, thrombin time, and fibrin degradation product levels are the distinguishing hallmark of thrombotic thrombocytopenic purpura. It is often these coagulation studies that permit these two disorders to be differentiated.

Thrombotic thrombocytopenic purpura is usually regarded as a primary disorder (although some cases are secondary to drugs), whereas DIC is regarded as secondary to some other disorder.

Trousseau syndrome

Trousseau syndrome is considered to be chronic compensated DIC. This distinct syndrome is closely associated with adenocarcinoma of any stage.[12]

Clinical features of Trousseau syndrome include recurrent migratory thrombophlebitis with limited response to warfarin. Typically the syndrome promptly relapses when heparin therapy is stopped.[13] Laboratory data may mimic those seen in acute DIC.

Therapy is challenging, as patients with this condition may simultaneously experience thrombosis (venous and arterial) and hemorrhage. Survival hinges on heparin therapy, sometimes requiring unusually high doses which, in turn, may lead to hemorrhage.

Severe liver disease

Acute or chronic hepatic failure results in decreased synthesis of hemostatic factors. Thrombocytopenia is common in patients with cirrhosis secondary to portal hypertension with hypersplenism. In addition, decreased degradation of activated coagulation factors results in prolongation of clotting times, and synthesis of coagulation factors is drastically decreased, further prolonging the prothrombin time and activated partial thromboplastin time. Decreased clearance of fibrin degradation products results in their accumulation.

Characteristically, the laboratory perturbations are more worrisome than the modest hemorrhagic potential of these chronically ill patients. Brisk bleeding in hepatic disease is more often structural (eg, due to gastritis, ulcers, or varices).

HELLP syndrome

Discriminating between HELLP syndrome and DIC can be challenging or impossible, as HELLP syndrome can deteriorate to DIC.[14] There is no clear line separating these two conditions of pregnancy. However, hypertension is rare in DIC but fairly common in HELLP.[15]

In patients with severe or especially deteriorating findings, the treatment is to promptly deliver the fetus and placenta. One must work closely with obstetrical colleagues to determine the optimal timing of delivery.

CONSEQUENCES OF DIC: MULTIPLE ORGAN DYSFUNCTION

In DIC, it is the host's response to an underlying pathologic condition that leads to the progression to multiple organ dysfunction syndrome that is often life-threatening or fatal.

At the microcirculatory level, both thromboses and hemorrhage into the organ result in ischemia, tissue damage, and progressive organ failure. Additionally, hypotension with resultant impaired organ perfusion exacerbates organ dysfunction.

Due to sequential and progressive decline of organ function, a variety of laboratory perturbations and clinical manifestations may develop (TABLE 3):

- Liver function may deteriorate and jaundice may develop.
- Cardiac abnormalities may be demonstrated by elevation in serum cardiac enzymes, cardiac rhythm disturbances, or both.
- Renal function declines, as evidenced by oliguria and rising serum creatinine levels or blood urea nitrogen values, or both.
- Pulmonary insult leads to diffuse alveolar hemorrhage and adult respiratory distress syndrome.
- Central nervous system abnormalities include altered mental status, seizures, and focal neurologic deficits.
- Gastrointestinal injury manifests mainly through mucosal ulcerations with consequent bleeding.
- Adrenal insufficiency may result from adrenal gland infarction with subsequent hemorrhagic necrosis.
- Skin manifestations include petechiae and purpura fulminans from hemorrhagic skin necrosis.

Although it is impossible to predict accurately whether DIC will be lethal, the onset of multiorgan dysfunction syndrome has been shown to forecast significant mortality.

It is far more effective to remove a necrotic bowel than to infuse blood products

TREAT THE UNDERLYING CAUSE

DIC is always secondary to an underlying disorder that is usually clinically obvious. Therapy directed at the laboratory manifestations of DIC may, at best, stabilize the patient but not change the course of the underlying disorder.

It is therefore important to recognize the underlying cause of DIC and to treat that cause. Mant and King[11] found that 85% of their patients with acute, severe DIC died and that the underlying disease, rather than DIC, was responsible for death.

There is no consensus on the optimal treatment of DIC, nor should consensus be expected, given the long list of possible causes.

In localized DIC, the treatment strategy may be apparent: evacuation of the uterus is the appropriate treatment for DIC secondary to obstetric emergencies, drainage of an abscess will lead to improvement in DIC caused by bacterial sepsis, and debridement of devitalized tissue in trauma and burn patients will help control DIC.

In most patients with DIC, supportive measures are mandatory. Resuscitation of the patient's circulatory system is essential to enhance perfusion.

Blood product replacement for patients with bleeding

Supportive treatment for a patient with active bleeding as a major symptom of DIC includes replacement therapy when the platelet count or clotting factors reach critical thresholds. Replacement therapy is typically indicated only in patients with active bleeding or at high risk for bleeding, not those with laboratory abnormalities alone.

Platelet transfusion is indicated for patients with active hemorrhage whose platelet counts are below 50×10^9/L. Transfusion of 1 to 2 units per 10 kg per day to maintain platelet counts in the range of 50 to 75×10^9/L is practical. Higher levels are not useful.

Cryoprecipitate infusion replaces fibrinogen and is reasonable in patients with active bleeding with fibrinogen levels lower than 50 to 60 mg/dL. Typically, 10 units of cryoprecipitate is adequate to achieve a desired fibrinogen level above 100 mg/dL.

Depletion of other coagulation factors is usually not clinically significant until levels of these factors are below 25% of normal levels, a situation that actually rarely happens.

Infusion of fresh frozen plasma to replace depleted clotting factors may help hemostasis, though the best way to replace fibrinogen is with cryoprecipitate.

Restoring coagulation inhibitors

Another therapeutic option that seems reasonable is to restore thrombin inhibitors to physiologic levels.

Giving fresh frozen plasma as a source of antithrombin III, protein C, or protein S is not practical, given the short half-life of these factors in the plasma.

In preliminary studies, infusion of recombinant human activated protein C was successful in patients with severe sepsis.[16] Activated protein C may have both anticoagulant and anti-

inflammatory properties.

Don't delay definitive treatment

A common and serious error in the management of DIC is to waste time trying to correct abnormal laboratory values by giving blood product infusions prior to invasive procedures. It is more important to try to correct the actual cause of DIC.

For example, if DIC is due to bowel necrosis, it is far more effective to remove the bowel, thus correcting the cause of DIC, than to adjust laboratory values with fresh frozen plasma, cryoprecipitate, and platelets. These blood products can be given during and after the operation. Delaying this definitive treatment only allows for the process to progress to multiorgan dysfunction syndrome.

Little data for heparin, other anticoagulants

Giving heparin or other anticoagulants to reduce thrombin generation seems reasonable, given thrombin's central role in DIC, but the effectiveness of this treatment is controversial.

There is little clinical evidence to support the use of these agents in severe acute DIC. In fact, giving heparin in severe acute DIC increased the risk of hemorrhagic death in one series.[11]

However, in chronic DIC conditions such as Trousseau syndrome and abdominal aortic aneurysm, heparin is the mainstay of therapy to decrease thrombotic events. Since baseline coagulation tests are often abnormal in these subacute thrombotic forms of DIC, standard heparin may be started empirically (8 to 10 units/kg/hour by constant intravenous infusion) and monitored by the activated partial thromboplastin time or plasma heparin level.

Blockade of the fibrinolytic system with agents such as epsilon-aminocaproic acid is generally not recommended in DIC, as such blockage may well reveal the gravity of the underlying thrombotic potential. In patients with massive fibrinolysis and extreme hemorrhage, epsilon-aminocaproic acid can be tried (4 g intravenously as a loading dose, followed by 1 g intravenously every 2 hours for 24 hours), but only after concurrent heparin therapy has been started.

REFERENCES

1. **Berckmans RJ, Nieuwland R, Boing AN, Romijn FP, Hack CE, Sturk A.** Cell-derived microparticles circulate in healthy humans and support low grade thrombin generation. Thromb Haemost 2001; 85:639–646.
2. **Semeraro N, Colucci M.** Tissue factor in health and disease. Thromb Haemost 1997; 78:759–764.
3. **Carr JM, McKinney M, McDonagh J.** Diagnosis of disseminated intravascular coagulation. Role of D-dimer. Am J Clin Pathol 1989; 91:280–287.
4. **van Gorp EC, Suharti C, ten Cate H, et al.** Review: infectious diseases and coagulation disorders. J Infect Dis 1999; 180:176–186.
5. **Hansen K, Singer DB.** Asplenic-hyposplenic overwhelming sepsis: postsplenectomy sepsis revisited. Pediatr Dev Pathol 2001; 4:105–121.
6. **Gamper G, Oschatz E, Herkner H, et al.** Sepsis-associated purpura fulminans in adults. Wien Klin Wochenschr 2001; 113:107–112.
7. **Selladurai BM, Vickneswaran M, Duraisamy S, Atan M.** Coagulopathy in acute head injury—a study of its role as a prognostic indicator. Br J Neurosurg 1997; 11:398–404.
8. **Rickles FR, Levine MN.** Hemostatic and thrombotic disorders of malignancy. In: Kitchens CS, Alving BM, Kessler CM, editors. Consultative hemostasis and thrombosis. Philadelphia: W.B. Saunders; 2002: 325–341.
9. **Barbui T, Finazzi G, Falanga A.** The impact of all-trans-retinoic acid on the coagulopathy of acute promyelocytic leukemia. Blood 1998; 91:3093–3102.
10. **Weiner CP.** The obstetric patient and disseminated intravascular coagulation. Clin Perinatol 1986; 13:705–717.
11. **Mant MJ, King EG.** Severe, acute disseminated intravascular coagulation. A reappraisal of its pathophysiology, clinical significance and therapy based on 47 patients. Am J Med 1979; 67:557–563.
12. **Sack GH, Levin J, Bell WR.** Trousseau's syndrome and other manifestations of chronic disseminated coagulopathy in patients with neoplasms: clinical, pathophysiologic and therapeutic features. Medicine 1977; 56:1–37.
13. **Bell WR, Starken NF, Tong S, et al.** Trousseau's syndrome: devastating coagulopathy in the absence of heparin. Am J Med 1985; 79:423–430.
14. **de Boer K, Buller HR, ten Cate JW, Treffers PE.** Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets. Br J Obstet Gynaecol 1991; 98:42–47.
15. **Egerman RS, Sibai BM.** Imitators of preeclampsia and eclampsia. Clin Obstet Gynecol 1999; 42:551–562.
16. **Bernard GR, Vincent JL, Laterre PF, et al.** Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344:699–709.

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