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Pathogenesis, diagnosis, and management of disseminated intravascular coagulation: a literature review

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Abstract. – *Background:* Disseminated Intravascular Coagulation (DIC) is an acquired syndrome characterized by systemic intravascular activation of coagulation, leading to deposition of fibrin in the circulation, occurring in the course of severe diseases.

***Objective:* To review literature for articles that focus on the pathogenesis, diagnosis, and management of DIC.**

***Information Sources:* Selected articles from the Index Medicus data base.**

***State of the Art:* Recent studies have elucidate the pathogenic pathways that can trigger DIC. However, clinical and laboratory diagnosis of the syndrome remains difficult, as there is no single laboratory test, sensitive and specific enough, to allow a definitive diagnosis of DIC. Cornerstone for the treatment of DIC remains the optimal management of the underlying disorder. However, therapeutic interventions based on our present knowledge of the pathogenesis of DIC may be appropriate.**

***Conclusion:* Recent research on DIC, resulted in the development of diagnostic algorithms for the diagnosis of the syndrome and better supportive therapeutic strategies.**

Key Words:

Disseminated intravascular coagulation, Bleeding, Tissue factor, Multi organ failure, Fibrin, Scoring system.

Introduction

Disseminated Intravascular Coagulation (DIC) is a disorder that is characterized by the systemic intravascular activation of the coagulation system, simultaneously leading to intravascular thrombi, compromising an adequate blood supply to the organs, and to bleeding as consequence of exhaustion of the platelets and coagulation factors[1]. It was first described by Landois in 1875 after giving dogs human blood intravenously and found hyaline thrombi in the vessels of the mesentery[2].

The clinical features of DIC include spontaneous or induced bleeding complications and thrombotic complications, whereas multiple organ failure may be in part a result of intravascular fibrin formation. In addition, the generation of multiple proteolytically active enzymes of the clotting cascade may enhance inflammatory activity, which may worsen the systemic inflammatory syndrome[3]. In fact, DIC is both a bleeding and thrombotic disorder.

A variety of disorders, including infections or inflammatory conditions and malignant disease, can lead to activation of coagulation. In many cases this activation of coagulation may not lead to clinical complications and may not even be detected by routine laboratory tests[4]. However, if activation of coagulation is sufficiently strong, a decreasing platelet count and prolongation of global clotting time may become manifest[4].

The management of DIC is primarily directed at treating the underlying disease, but supportive care may be important. This care may consist of supplementing the depleted coagulation factors and endogenous coagulations inhibitors, and of inhibiting coagulation by various anticoagulant strategies, or by manipulating the fibrinolytic system[5].

This study reviews literature for articles that focus on the pathogenesis, diagnosis, and management of DIC.

Pathogenesis

DIC's frequency for hospitalized patients has been counted 1.72%[6]. Underlying diseases, frequently associated with DIC in these patients, are

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acute promyelocytic leukemia, fulminant hepatitis, and sepsis[6]. Most patients with DIC have sepsis, non-Hodgkin's lymphoma or hepatoma. Table I summaries diseases that can be associated with DIC.

The initial phase of DIC consists of formation of microvascular thrombosis in kidneys and lungs with several degree of acute renal failure and adult respiratory distress syndrome (ARDS). In the second phase, which may supervene rapidly, wide-spread activation of fibrinolysis lysis microthrombi but destroys coagulation factors and platelets, all of which are rapidly consumed and depleted. This severe consumption coagulopathy leads to uncontrolled bleeding from wounds and spontaneous haemorrhage into tissue, gut and brain.

Organ failure due to hypercoagulopathy is considered an important aspect of the pathology of DIC[6]. Studies have indicated that several factors such as leukocyte activation, vascular endothelial cell injury and release of chemical mediators are involved in organ failure[7,8].

Tissue factor can trigger the extrinsic pathway of coagulation. Its activity in peripheral blood is markedly elevated upon tissue injury and activation of monocytes[6]. The high tissue factor activity results in the transformation of prothrombin to form fibrin thrombus. Increased tissue factor production is considered the most important for the onset of DIC[6]. Tissue factor is significantly high in leukemic cells of patients with DIC suggesting that DIC in leukemia is caused by elevated tissue factor in leukemic cells[6,9]. Tissue factor is also significantly high in DIC patients with solid tumors such as gastric cancer[6].

Table I. Conditions Associated with DIC.

Infections
Bacterial
Gram negative bacilli
Staphylococci
Streptococci
Meningococci
Viral
Arbovirus
Varicella
Variola
Rubella
Mycotic
Acute histoplasmosis
Parasitic
Malaria
Kala-Azar
Rickettsial
Rochy Mountain spotted fever
Obstetrical syndromes
Abruptio placentae
Amniotic fluid embolism
Retained dead fetus
Neoplasms
Acute promyelocytic leukemi
Adenocarcinomas
Hemolysis
Intravascular hemolysis
Fat embolism
Trauma
Burn
Aortic aneurysm
Kasabach-Merritt syndrome
Hemolytic uremic syndrome
Acute glomerulitis

DIC in Sepsis

Infectious disease, in particular septicaemia, is the most common clinical condition associated with DIC. Although virtually all microorganisms can cause DIC, bacterial infection is most frequently related to the development of the syndrome[1]. Clinically overt DIC may occur in 30 to 50% of patients with Gram negative sepsis[10-12]. Contrary to widely held belief, clinically over DIC appears to be as common in patients with Gram positive as in those with Gram negative sepsis[13].

The mechanisms involved in the onset of DIC associated with sepsis are different from that associated with leukemias and solid cancers[6]. Patients with septicemia associated with DIC frequently have elevated levels of lipopolysaccharides[6]. Moreover, in burn injury, trauma and major surgery, blood and vascular endothelial cells are activated by various stimuli and chemical mediators such as inflammatory cytokines[14,15] produced by activated leukocytes. In sepsis, lipopolysaccharides results from infection by Gram-negative bacteria. Conversely, septic infection with Gram positive bacteria results in peptidoglycan exposure which can then activate the toll-like receptor[16,17]. Activation of toll-like receptor in turn, stimulates nuclear factor-kappa B, which stimulates the production of various inflammatory cytokines including tissue factor[14,15].

DIC is mediated by several proinflammatory cytokines[18,19]. The principal mediator of activation of coagulation appears to be interleukin-6, and it is the pivotal mediator of the dysregulation of the physiologic anticoagulation pathways and the fibrinolytic defect[1]. Effects of the above processes cause microcirculation failure culminating in DIC and multiorgan failure[6].

The main defence factors against DIC are the fibrinolytic system, several protease inhibitors, and vascular endothelial cells[6]. Studies in animal models and in patients with DIC have clarified the pathogenetic pathways of the disorder. The systemic formation of fibrin results from increased generation of thrombin, the simultaneous suppression of physiologic anticoagulation mechanisms, and the delayed removal of fibrin as a consequence of impaired fibrinolysis[1].

DIC in Acute Leukemia

Malignancy is associated with hypercoagulable state and high risk for thrombohemorrhagic complications[20]. Clinical manifestations can vary from localized deep venous thrombosis, more frequent in solid tumors, to life-threatening bleeding because of DIC. The bleeding or thrombotic manifestations represent the "tip of the iceberg" of a condition of subclinical or chronic DIC, typically associated with all types of malignancy[20]. Indeed, very commonly patients with solid tumors and leukemias present with abnormalities in laboratory tests of blood coagulation, even without clinical manifestations[20]. These abnormalities demonstrate different degrees of blood clotting activation and characterize the so-called hypercoagulable state in these subjects[21-23].

Bleeding manifestations are frequent in acute leukemias, particularly in acute myeloblastic leukemia, and are prominent of an early stage of disease[20]. The abnormalities of the blood clotting system underlying the clinical pictures of the coagulopathy well-described in acute promyelocytic leukemia, include hypofibrinogenemia, increased levels of fibrin degradation products, and prolonged PT and PTT[24]. These laboratory parameters often become more abnormal with the initiation of cytoxic chemotherapy, resulting in severe hemorrhagic complications. The results of new tests to detect enzyme inhibitor complexes and activation peptides demonstrate that the levels of well-known plasma markers of clotting activation like the prothrombin fragment F1 + 2, the thrombin-antithrombin complex, and the fibrinopeptide A are abnormally elevated in this condition[25,26]. In addition, plasma markers indicating ongoing hyperfibrinolysis, including high levels of fibrin degradation products and urokinase plasminogen activator, together with low levels of plasminogen and a_2-antiplasmin, are present[27-29]. New laboratory tests for subclinical DIC clearly show that thrombin generation is a constant finding in acute leukemia[20].

The major determinants for the pathogenesis of the coagulopathy of acute leukemia are (1) factors associated with leukemia cells, including the expression of procoagulant, finrinolytic, and proteolytic properties, and the secretion of inflammatory cytokines, in other word, interleukin-1β and tumor necrosis factor; (2) cytoxic therapy; and (3) concomitant infectious complications[20].

DIC in Trauma Patients

The trauma patients' survival depends in the ability to control hemorrhage and support vital organ by preventing multi organ dysfunction syndrome after DIC[30]. Hemostatic activity is basically confined to the area of the injury. Occasionally, control mechanisms fail to restrict the hemostatic processes to the area of tissue damage, and they become disseminated throughout the systemic circulation, which causes DIC[30].

The intrinsic pathway of coagulation does not appear to play an important role for the activation of coagulation in DIC[31]. The consensus is that the function of the contract system is to generate bradykinin, a potent inducer of local edema and systemic hypotension[8,31]. Several lines of evidence point to the pivotal role of the tissue factor-depended pathway in the initiation of thrombin generation[30]. This concept is true for DIC patients after trauma. Continuously higher tissue factor levels were observed in DIC patients compared with non-DIC patients on the day of trauma and the days 1 through 4 after admission[30,32]. The results suggest extensive activation of the extrinsic coagulation pathway in post-trauma DIC[30].

Tissue factor pathway inhibitor, protein C, and antithrombin, three major physiological anticoagulants were found greatly affected in post-trauma DIC patients[30]. Gando et al[32] found that an activated tissue factor-depended pathway is not sufficiently prevented by the normal tissue factor pathway inhibitor in post-trauma patients with DIC. They also showed that when trauma patients were complicated with DIC, the protein C activity and the antigen levels showed significantly lower values than those for non-DIC patients[G33]. Owings and Gosselin[34] showed that also antithrombin was significantly reduced in trauma patients.

Natural Inhibitors of Coagulation

Antithrombin

Natural inhibitors of coagulation like antithrombin, the protein C system and tissue factor pathway inhibitor play an important role in controlling the activation of coagulation during DIC[35]. Furthermore, they may not only influence coagulation but also attenuate inflammatory responses during sepsis[35]. All major physiologic anticoagulants, antithrombin III, protein C, and tissue factor pathway inhibitor appear to be affected in patients with DIC. Low circulating levels of antithrombin and protein C have been associated with poor outcome[35]. Replacement therapy with antithrombin, activated protein C, and tissue factor pathway inhibitor has been shown to attenuate thrombin generation and to reduce mortality in experimental sepsis models[35].

Antithrombin is an important physiological regulator of blood coagulation that affects the intrinsic, extrinsic, and common pathways of coagulation [35]. It has the capacity to inhibit thrombin, factors IXa, Xa, XIa, and XIIa, and the factor VIIa-tissue factor complex[36,37]. In situations associated with DIC, such as sepsis, circulating antithrombin levels are decreased due to increased consumption and degradation by elastase released from activated neutrophiles[38,39]. In sepsis, low antithrombin levels are associated with increased mortality[40].

Because antithrombin has shown promising results in animal models of DIC, the use of antithrombin concentrate in patients has been studied intensively[35]. A number of controlled trials, most of them concerning patients with sepsis, have been conducted[41-47]. Two meta-analyses of these trials were performed that suggested a decreased mortality in patients with sepsis when antithrombin was administrated[8,45]. One trial compared antithrombin infusion to a synthetic protease inhibitor in obstetric patients with DIC[48] and found that a single infusion of antithrombin was more effective in controlling the symptoms of DIC, but without effect on survival. Administration of high doses of antithrombin, aiming at plasma levels of more than 120%, appears to be safe and well-tolerate[43]. Therefore, physicians involved in the care of patients with sepsis and DIC may consider antithrombin replacement an optional therapy that is well-tolerated[35].

The Protein C System

The protein C system is an important regulator of blood coagulation initiated by thrombin, and serves as an on-demand mechanism for limiting the coagulation response to injury[35]. The importance of the protein C system is illustrated by the severe thrombotic complications seen in patients with deficiencies of members of this pathway[35]. The protein C system is impaired during sepsis because of different mechanisms. First, circulating cytokines can induce downregulation of thrombomodulin and endothelial cell protein C receptor on endothelial cells, resulting in decreased activation of C protein[49-51]. Endothelial cell thrombomodulin activity may also be reduced by proteolytic cleavage of thrombulin by neutrophil elastase[52] or by eosinophil products[53]. Furthermore, circulating protein C and protein S levels (activated protein C activity is facilitated by its cofactor protein S) are decreased during sepsis, probably because of increased consumption[54]. A multicenter randomized and placebo-controlled trial[55] involving 1690 patients with systemic inflammation and organ failure, about half of whom were treated with activated protein C, revealed an absolute risk reduction of 6.1% ($p = 0.005$) in favor of the treated group. Because protein S levels may also be low in patients with sepsis and DIC, replacement therapy with protein S might be useful as well[35].

Tissue Factor

In most instances, tissue factor exposed to the circulation is the sole culprit underlying the initiation of DIC[56]. It is well established that tissue factor serves as physiological trigger of blood coagulation[57,58]. It is a membrane glycoprotein synthesized as a 295 amino acid polypeptide, including a leader sequence. In its mature form consists of 263 amino acids residues organized into extracellular domain (219 residues), a transmembrane segment (23 residues), and a cytoplasmic tail (21 residues)[59].

The rationale for use of tissue factor pathway inhibitor for the treatment of DIC stems from the following observations: (1) the tissue factor pathway plays a pivotal role in the initiation of coagulation in DIC, (2) tissue factor pathway inhibitor is the major physiological inhibitor of the tissue factor pathway, and (3) endothelial cells produce or release tissue pathway inhibitor in response to injury[60]. Administration of exogenous tissue factor pathway inhibitor in disease states associated with DIC has been studied in many animal models[35]. Experience with recombinant tissue factor pathway inhibitor administration in humans is limited to studies with healthy volun-

teers that showed that it was safe, tolerable, and effective in inhibiting the endoxin-induced thrombin generation[61,62].

Natural Anticoagulant as Modulators of the Inflammatory Response

Natural anticoagulants can attenuate the coagulant response, reduce the clinical signs of DIC, and in some cases, improve survival in septicemia[35]. Experimental evidence suggests that the reduction in mortality may not be caused by the inhibition of coagulation itself but may rather be the result of diminished inflammatory responses[35]. The demised inflammatory response could be a direct result of preventing coagulation, because if has been shown that different activated coagulation factors such as thrombin, factor VIIa, and factor Xa can active cells to release cytokines[63]. However, although antithrombin, protein C, and tissue factor pathway inhibitor[64-66] protected against DIC, as well as mortality, alternative anticoagulant treatments with heparin[67] and active site-inhibited factor Xa[68] also effectively prevented the activation of coagulation in lethal primate models of sepsis, but without effect on lethality. Thus, it appears that other, noncoagulant functions of the natural coagulation inhibitors are involved in their modulation of the inflammatory response[35]. In fact, antithrombin has direct anti-inflammatory actions, independed of coagulation factors by an unknown mechanism[35], the protein C system has anti-inflammatory effects[35], and several studies have shown that tissue factor pathway inhibitor inhibits factor VIIa which can induce proinflammatory changes in mononuclear cells[69].

Fibrinolysis and Fibrin Degradation Products

Many studies indicate that the fibrinolytic system is largely suppressed at the time of maximal activation of coagulation in DIC[1]. This inhibition is caused by a sustained increase in plasma level on plasminogen activator inhibitor 1, the principal inhibitor of the fibrinolytic system[70,71]. Clinical studies have confirmed that suppression of fibrinolysis is mediated by plasminogen activator inhibitor type 1 and show that although there is some fibrinolytic activity in response to the formation of fibrin, the level of this activity is too low to counteract the systemic deposition[1,12,72,73].

Studies in experimental models for sepsis, the most common cause of DIC, have put forward the concept of a procoagulant state that is characterized by thrombin generation exceeding that of plasmin[74]. Many studies have shown activation of the fibrinolytic system in patients with sepsis, as evidenced by increased levels of plasmin-a_2-antiplasmin complexes[75,76]. Similar increases of these complexes have been observed in non-sepsi-related DIC[77,78]. Yet, most of these patients have a procoagulant state because the increase of thrombin-antithrombin complexes in general is more pronounced. In addition, levels of plasminogen and a_2-antitplasmin are low in most patients and correlate to some extent with outcome [35]. However, whether this only reflects consumption or decreased synthesis because of a negative phase behavior remains to be established[79]. Finally, levels of plasminogen activator inhibitor type 1 are generally very high in patients with sepsis[35]. These levels have consistently been found to correlate with outcome[80,81] also in patients with DIC due to causes other than sepsis. Interestingly, some studies have shown that administration of tissue-type plasminogen activator to animals with inflammatory conditions can reduce inflammation and improve some signs of organ failure, suggesting that enhancement of fibrinolysis may be beneficial in multiple organ failure[74].

Studies in sepsis models have led to the hypothesis that inhibition of fibrinolysis by plasminogen activator inhibitor type 1 contributes to the procoagulant state in sepsis[74]. Although the precise mechanisms for these beneficial effects of the clotting inhibitors are far from clear, initial experience in patients with sepsis indicates that they may attenuate sepsis in humans as well[74].

Thrombin cleaves fibrinopeptides from fibrinogen, forming fibrin monomer that rapidly polymerizes to form a clot[83]. Small amounts can circulate in plasma as soluble fibrin which may have a complex composition and include fibrinogen and a variable amount of cross-linking[83]. Plasmic degradation of cross-linked fibrin forms a heterogeneous group of degradation products reactive in assays for D-dimer, and their levels provide a measure of the account of fibrin formation and lysis[83]. Marked elevations of fibrin(ogen) degradation products are a constant finding in experimental animal models of DIC. In human models of DIC resulting from endotoxin infusion, D-dimer is elevated early, and high levels persist, reflecting lysis of microvascular

fibrin deposits[83]. Elevated levels of D-dimer and soluble fibrin are very sensitive for the diagnosis of DIC, and a normal level has a high negative predictive value[83]. Moreover, serial monitoring of soluble fibrin or D-dimer assays may be of value in evaluating the response to therapy[83]. Depending on the assay and the level chosen to distinguish normal and abnormal, their sensitivities range from approximately 90 to 100%[84-88]. Therefore, all or near all patients with DIC should have an elevated fibrin degradation product or soluble fibrin level. Fibrin(ogen) degradation products, D-dimer and soluble fibrin assays have greater sensitivity than specificity, because processes other than DIC may cause elevations[83]. For instance, both liver disease and renal insufficiency may cause an elevation in fibri(ogen) degradation product and D-dimer levels[89,80]. Because of this, these assays should never be employed alone but rather should be used in combination with other markers[83].

Clinical Picture

Patients with DIC may present with manifest thromboembolic disease or with clinically less apparent microvascular thrombosis, which predominantly exhibits as multiple organ dysfunction[8,91]. According to this, DIC should be seen as a contributing factor to organ failure, but alternative views suggest that DIC is merely a consequence of organ failure (failure of the microvasculature, comprising deranged endothelial cells. Stimulated blood cells, and an activated coagulation system as a result)[94]. In fact, both mechanisms may probably play a role.

Alternatively, severe bleeding may be the leading symptom. Quite often a patient with DIC has simultaneous thrombosis and bleeding, which does not facilitate a clinician's choice for the appropriate therapy[92]. In fact, both thrombosis and bleeding may occur at different locations and in varying intensity. The thrombotic spectrum ranges from laboratory signs of hypecoagulability without significance to vast intravascular deposition of fibrin, which may compromise the circulation[92]. Similarly, the intensity of bleeding spans from mild blood loss that is only present on injury to spontaneous, massive, and life-threatening bleeding[92].

In most situations the most frequent underlying cause of DIC is infection[92]. Clinically overt DIC may occur in 30 to 50% of patients with gram-negative sepsis[10-12]. However, contrary to widely held belief, clinically overt DIC appears as common in patients with gram-positive sepsis as it is in those with gram negative sepsis[13].

Polytrauma, because of physical force or burns or induced by heat stroke, may result in DIC because of combination of mechanisms, including hemolysis, endothelial activation, release of tissue material in the circulation (fat, phospholipids), and acidosis because of hypoperfusion[92].

There is ample evidence for a procoagulant state in virtually all patients with advanced malignant disease; however, the incidence of overt DIC appears to be much lower[93]. The exact incidence of DIC in patients with solid tumors cannot be inferred from the literature, but in patients presenting with leukemia can be diagnosed in 15 to 20%[92,94].

Vascular disorders, such as large aortic aneurysms or giant hemangiomas (Kasabach-Merritt syndrome), may result in local activation of coagulation[14,15,95]. Signs of DIC have also been associated with other vascular lesions, such as the Klippel-Trenaunay syndrome, hemangiomas of the liver and the spleen, hemangioendotheliosarcoma, and Osler's disease[96-100]. DIC may also be established in small proportion of patients with aneurysms of large vessels, such as the aorta. In patients with giant hemangiomas, an incidence of clinically important DIC up to 25% has been reported[92], but in more commonly occurring aortic aneurysms, recent series showed an incidence of systemic activation of coagulation in only 1% of cases[15].

Pre-eclampsia is the most common obstetric condition associated with activation of blood coagulation resulting in macroscopic fibrin deposits in various organs in severe cases[101,102]. Acute DIC occurs in placental abruption and amniotic fluid emboli[103]. Women surviving acute amniotic fluid emboli are at high risk (50% or more) of developing DIC, within 4 hours after the insult[104].

Diagnosis

The Scientific Standardization Committee of the International Society of Thrombosis and Haemostasis proposed that "DIC is an acquired syndrome characterized by intravascular activation of coagulation with loss of localization arising from different causes. It can originate from

and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction"[105].

Until today, no single laboratory test or a combination of tests is available which is sensitive and specific enough, to allow a definitive diagnosis of DIC. However, in most cases the diagnosis can reliably be made by taking into consideration the underlying disease and a combination of laboratory findings[106]. The recognition of the pivotal role played by thrombin in the pathophysiological process of DIC has led to the development of numerous assays centered around the detection of its generation (e.g., prothrombin fragment 1 + 2, thrombin-antithrombin complexes), its activation of the protein C and fibrinolytic pathways (e.g., activated protein C and inhibitor and plasmin-antiplasmin complexes), the consequent end products of its activity (e.g., fibrinopeptide A, soluble fibrin)[107]. Sensitive markers are thrombin-antithrombin complex, F1 + 2, D-dimer, soluble fibrin, and activated protein C – protein C inhibitor complex[108].

In routine setting, a diagnosis of DIC may be made by a combination of platelet count, measurement of global clotting times [activated partial thromboplastine time (aPTT), and prothrombin time (PT)], measurement of antithrombin III and/or 1 or 2 clotting factors, and a test for fibrin degradation products[1]. In clinical practice the disorder can be diagnosed on the basis of the following findings: an underlying disease known to be associated with DIC, an initial platelet count of less than 100,000 per cubic milliliter or a rapid decline in platelet count, prolongation of clotting times, such as the PT and aPTT, elevated INR, the presence of fibrin-degradation products in plasma, and low levels of coagulation inhibitors such as antithrombin III[1]. It should be emphasized that generally serial coagulation tests are more helpful than single laboratory results in the establishing the diagnosis DIC[106]. Recently has been described an atypical clotting profile as analyzed by light transmittance changes on the aPTT or PT[109,110]. This atypical waveform occurs independently of prolongation in the clotting times and, through prospective studies, has been shown to be a simple, rapid, and robust indicator of DIC with a sensitivity and specificity of greater than 90%[107,111]. It has also been characterized as an early indicator of impending DIC (pre-DIC), with monitoring and prognostic implications in the critical care setting.

The Japanese Ministry of Health and Welfare has developed a scoring system with laboratory tests for the diagnosis of DIC[112]. A cumulative score of 7 or greater is indicative of DIC. Based on modification of the criteria of the Japanese Ministry scoring, the International Society on Thrombosis and Hemostasis proposed a 5-step diagnostic algorithm[105] (Table II). A score equal or more than 5 is compatible with DIC, whereas a score of less than 5 may be indicative (but is not affirmative) for non-overt DIC[106].

Management

It is well accepted that the cornerstone for the treatment of patients with DIC is the management of the underlying disorder. However, therapeutic interventions based on our present knowledge of the pathogenesis of DIC may be appropriate.

Plasma and Platelets

The consumption of coagulation factors and platelets in DIC patients increases the risk of bleeding. Treatment with plasma or platelet concentrates is guided by the clinical condition of the patients and should not be instituted on the basis of laboratory finding alone[5]. The efficacy of treatment with plasma and platelets has been shown in patients with low laboratory levels who require an invasive procedure[93,113]. There is no evidence to support the prophylactic administra-

Table II. Diagnostic algorithm for the diagnosis of overt DIC[105].

Risk assessment: Does the patient have a underlying disorder known to be associated with overt DIC? If yes: proceed; if no: do not use this algorithm
Order global coagulation tests (platelets count, PT, fibrinogen, soluble fibrin monomers or fibrin degradation products)
Score global coagulation test results
Platelet count (> 100 = 0; < 100 = 1; < 50 = 2)
- Elevated fibrin-related marker (e.g. soluble fibrin monomers/fibrin degradation products) (no increase = 0; moderate increase = 2; strong increase = 3)
- Prolonged PT (< 3 sec = 0; > 3 sec but < 6 sec = 1; > 6 sec = 2)
- Fibrinogen level (> 1 g/L = 0; < 1 g/L = 1)

Calculate score
If ≥ 5: compatible with overt DIC; repeat scoring daily. If < 5 suggestive (non affirmative) for non-overt DIC; repeat next 1-2 days

tion of platelets or plasma to patients who are not bleeding and who are not at high risk of bleeding[1].

To sufficiently correct the coagulation defect, large volumes of plasma may be needed, up to 6 units per 24 hours[1]. The use of coagulation factors concentrates may overcome this need; however, they may be contaminated with traces of activated coagulation factors and may therefore be particularly harmful for patients with DIC[5]. Cryoprecipitate, which contains fibrinogen as well as factor VIII, von Willebrand factor, factor XIII, and fibronectin, is also used as replacement therapy, without however any support from controlled trials[5].

Anticoagulants

Theoretically, interruption of coagulation should be of benefit in patients with DIC. Indeed, experimental studies have shown that heparin can partially inhibit the activation of coagulation in cases that are related to sepsis or other causes[1]. Adequate prophylaxis is also needed to eliminate the risk of venous thromboembolism[1]. Heparin has been used for the treatment of DIC since 1959[114]. Animal studies have shown that this drug can inhibit the activation of coagulation in experimental septicemia but does not affect mortality[115,116]. Heparin has been shown to have a beneficial effect in small, uncontrolled studies of patients with DIC, but not in controlled clinical trials[117,118]. Although the safety of heparin in patients with DIC who are prone to bleeding has been debated, clinical studies have not shown that treatment with heparin significantly increased the incidence of bleeding[1]. Taken together, there is no sound of evidence in favor of the use of heparin as routine therapy in patients with DIC[5], but it is probably useful, particularly in those with clinically overt thromboembolism or extensive deposition of fibrin as occurs with purpura fulminans or acral ischemia[1].

Low Molecular Weight Heparin

Low molecular weight heparin has a decreased risk of bleeding while having at least the same antithrombotic potential as unfractioned heparin. Effective treatment of DIC has been reported in rabbits[119]. Successful treatment was also reported in 2 small uncontrolled studies in humans[120,121]. Furthermore, the effects of dalteparine sodium in the treatment of DIC have been studied in a multicenter, double-blind, randomized trial[122]. In this study, dalteparin sodium showed greater efficacy than unfractioned heparin in improving bleeding symptoms and in improving subjective organic symptoms score. Hence, from this study it may be postulated that low molecular weight heparin offers the benefit of decreased bleeding complications compared to unfractioned heparin in the treatment of DIC[5].

Hirudins

Recombinant hirudin appeared to be effective in treating DIC in animal studies[123-125]. However, no randomized controlled trial on the use of hirudin in patients with DIC is available. The high risk of bleeding may potentially limit its use in patients with DIC[5].

Coagulation Inhibitors

Antithrombin III is an important inhibitor of coagulation, and low levels in plasma are associated with increased mortality[40]. The administration of this inhibitor in supraphysiologic concentrations reduced sepsis-related mortality in animals[126]. Several controlled trials, mostly in patients with sepsis, have shown beneficial effects in terms of improvement of DIC and some times organ function[43-45]. A meta-analyses of the trials showed a reduction in mortality from 56 to 44%[1]. The conclusion from the studies is that antithrombin III is able to improve DIC, but that benefit in terms of clinical outcome is less certain[5].

The depression of the protein C system may significantly contribute to the pathophysiology of DIC. Therefore, supplementation of activated protein C might potentially be of benefit[4]. In experimental sepsis studies, activated protein C was shown to be effective in reducing mortality and organ failure[66]. The clinical efficacy in severe sepsis was demonstrated in a large, randomized controlled trial[55]. Mortality was 24.7% in the activated protein C group as compared with 30.8% in the placebo group. Later studies confirmed the ability of activated protein C to normalize coagulation activation during severe sepsis[127]. However, activated protein C seems to be more effective in higher disease severity groups[4], and a prospective trial in septic patients with relatively low disease severity did not show any benefit of activated protein C[128].

Since tissue factor plays a key role in the initiation of coagulation during DIC, inhibiting its action could be of value in the treatment of DIC[5]. In an animal study[129], the infusion of recombinant tissue factor pathway inhibitor immediately

after endotoxin administration significantly inhibited the consumption of coagulation factors and platelets. Phase II clinical trials of recombinant tissue factor pathway inhibitor in patients with sepsis showed promising results, but a phase III trial did not show an overall survival benefit in patients who were treated with tissue factor pathway inhibitor[130-131].

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