Pathogenesis and General Management of Disseminated Intravascular Coagulation

Barnoyev Saidjon Sharifovich Bukhara State Medical Institute
Sharopov Umarxo`ja Ravshanovich Bukhara State Medical Institute

ABSTRACT

Systemic intravascular activation of coagulation, which results in the deposition of fibrin in the circulation, is the hallmark of disseminated intravascular coagulation (DIC), an acquired syndrome that develops during severe illnesses.

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

Purpose of the study: To audit writing for articles that attention on the pathogenesis, analysis, and the executives of DIC.

Materials and methods: It is now clear from recent research which pathogenic pathways can lead to DIC. However, there is still no single laboratory test that is sensitive and specific enough to allow for a clear diagnosis of DIC, making clinical and laboratory diagnosis of the disease challenging. The best possible treatment for the underlying disorder is still the cornerstone of DIC care. Nonetheless, treatment plans that take into account the pathophysiology of DIC as it is currently understood may be suitable.

Introduction. The coagulation system is systemically activated intravascularly in patients with disseminated intravascular coagulation (DIC), which concurrently cause intravascular thrombi, compromise the organs' ability to receive enough blood, and cause bleeding due to platelet and coagulation factor exhaustion1. After feeding dogs intravenous human blood, Landois discovered hyaline thrombi in the mesentery vessels, which led to the first description of it in 1875 [2].

While thrombotic and spontaneous or induced bleeding problems are among the clinical characteristics of DIC, intravascular fibrin production may also play a role in multiple organ failure. Moreover, the clotting cascade's production of several proteolytically active enzymes may increase inflammatory activity, exacerbating the systemic inflammatory syndrome [3]. In actuality, DIC is a thrombotic and bleeding illness. Activation of coagulation can result from a number of illnesses, such as infections, inflammatory conditions, and malignant disease. In certain situations, this coagulation activation might not even be noticed by standard laboratory testing4, much alone cause clinical consequences. However, a declining platelet count and an extension of the global clotting time may appear if coagulation is activated sufficiently strongly [4]. The main goal of DIC management is to treat the underlying

condition, while supportive care could also be crucial. This treatment could include replenishing the body's stores of depleted coagulation components and natural coagulation inhibitors, as well as preventing coagulation with a variety of anticoagulant techniques and fibrinolytic system manipulations [5].

This study searches the literature for publications that address the etiology, diagnosis, and treatment of diabetic eye disease.

Pathogenesis

The prevalence of DIC among hospitalized patients is 1.72% [6]. In these patients, fulminant hepatitis, sepsis, and acute promyelocytic leukemia are frequently linked with DIC [6]. The majority of DIC patients had hepatoma, non-Hodgkin's lymphoma, or sepsis. The development of microvascular thrombosis in the kidneys and lungs, along with varying degrees of acute renal failure and adult respiratory distress syndrome, constitute the early phase of diabetic kidney injury.

The second phase eliminates coagulation factors and platelets, which are all quickly eaten and exhausted, but may also quickly and widely activate fibrinolysis lysis microthrombi. Severe consumption coagulopathy causes spontaneous hemorrhage into tissue, the intestines, and the brain in addition to uncontrollably bleeding from wounds. Organ failure resulting from hypercoagulopathy is regarded as a significant component of DIC [6] disease. Numerous factors, including vascular enlargement, leukocyte activation, and organ failure is linked to damage to dothelial cells and the release of chemical mediators [7, 8].

Tissue factor has the ability to initiate the extrinsic coagulation pathway. Its peripheral blood activity is noticeably increased in response to tissue damage and monocyte activation6. Fibrin thrombus is formed when prothrombin is transformed into a high tissue factor activation. It is thought that increased tissue factor production plays the most significant role in the development of DIC [6]. Patients with DIC had significantly higher tissue factor in their leukemic cells, indicating that enhanced tissue factor in leukemic cells is the source of DIC in leukemia [6,9]. When solid tumors like stomach cancer are present in DIC patients, tissue factor is also noticeably elevated [6].

DIC in septic condition.

Septicaemia, in particular, is the most frequent clinical complication linked to drug-induced diarrhea. While almost any microbe has the ability to induce DIC, bacterial infection is typically linked to the onset of the syndrome [1]. Thirty to fifty percent of patients with Gram negative sepsis may experience clinically overt DIC [10–12].

Contrary to popular assumption, patients with Gram positive sepsis appear to have clinically over DIC just as frequently as those with Gram negative sepsis [13]. Different processes underlie the start of DIC linked to sepsis than those linked to leukemias and solid tumors [6]. Individuals suffering from DIC-related septicemia often exhibit higher lipopolysaccharides [6] levels. Furthermore, inflammatory cytokines [14,15] produced by activated leukocytes are among the stimuli and chemical mediators that activate blood and vascular endothelial cells after burn injury, trauma, and major surgery. Lipopolysaccharides are a consequence of Gram-negative bacterial infection in sepsis. On the other hand, septic infection with Gram-positive bacteria exposes peptidoglycan, which might subsequently activate the receptor that is toll-like [16,17]. The production of several inflammatory cytokines, including tissue factor, is stimulated by the activation of toll-like receptor, which in turn promotes nuclear factor-kappa B [14, 15].

Numerous proinflammatory cytokines mediate DIC [18,19]. Interleukin-6 seems to be the main mediator of coagulation activation. because it is the primary mediator of the fibrinolytic deficiency and the deregulation of the physiological anticoagulation pathways [1]. The aforementioned processes' effects result in microcirculation failure, which culminates in DIC and multiorgan failure [6].

Vascular endothelial cells [6], the fibrinolytic system, and a number of protease inhibitors are the primary defense mechanisms against DIC.

The pathogenetic mechanisms of DIC have been elucidated by research conducted on people and animal models. Increased thrombin production, concurrent suppression of physiological anticoagulation mechanisms, and delayed fibrin clearance as a result of compromised fibrinolysis1 all contribute to the systemic development of fibrin.

DIC in acute leukemia

Hypercoagulable condition and increased risk of thrombo-hemorrhagic consequences are linked to malignancy [20]. Clinical signs and symptoms may range from life-threatening bleeding due to DIC to localized deep vein thrombosis, which is more common in solid tumors. The thrombotic or bleeding symptoms are really the "tip of the iceberg" of a chronic or subclinical form of DIC that is usually linked to various forms of cancer [20]. In fact, abnormalities in laboratory blood coagulation tests are frequently observed in patients with solid tumors and leukemias, even in the absence of clinical manifestations [20]. These anomalies represent the so-called hypercoagulable state in these individuals and show varying degrees of blood clotting activation [21–23]. In acute leukemias, especially acute myeloblastic leukemia, bleeding symptoms are common and indicative of an early stage of disease [20]. Hypofibrinogenemia, elevated levels of fibrin degradation products, and extended PT and PTT [24] are among the anomalies of the blood clotting system that underlie the clinical features of the coagulopathy well-described in acute promyelocytic leukemia. Severe hemorrhagic problems frequently occur when cytoxic treatment is started because these laboratory parameters tend to become more abnormal. The prothrombin fragment F1 + 2, the thrombin-antithrombin complex, and the fibrinopeptide A are examples of well-known plasma markers of clotting activation that have abnormally elevated levels in this condition, according to the results of new tests to detect enzyme inhibitor complexes and activation peptides [25, 26]. Furthermore, there are plasma indicators that show continuous hyperfibrinolysis, such as low levels of plasminogen and a2-antiplasmin and high amounts of fibrin breakdown products and urokinase plasminogen activator [27–29]. Acute leukemia consistently exhibits thrombin production, as demonstrated by new laboratory techniques for subclinical DIC20.

The main factors that determine the pathogenesis of the coagulopathy associated with acute leukemia are: (1) leukemia cell-associated factors, such as procoagulant, finrinolytic, and proteolytic properties expressed, and the secretion of inflammatory cytokines, i.e., tumor necrosis factor and interleukin-1β; (2) cytoxic therapy; and (3) concurrent infectious complications [20].

DIC in traumatic patients

The ability of trauma patients to manage bleeding and sustain essential organs by averting multiorgan dysfunction syndrome following DIC [30] is critical to their survival. Hemostatic action is essentially limited to the site of the wound. DIC [30] is occasionally caused by control mechanisms that are unable to confine the hemostatic processes to the site of tissue destruction, allowing them to spread throughout the systemic circulation.

The activation of coagulation in DIC [31] does not seem to be significantly influenced by the intrinsic coagulation pathway. Everyone agrees that the contract system's job is to produce bradykinin, which is a strong inducer of systemic hypotension and local edema [8,31]. The tissue factor-dependent pathway plays a crucial role in the start of thrombin production, according to multiple lines of evidence [30]. After trauma, this idea holds true for DIC patients.

On the day of trauma and the first four days following admission, DIC patients' tissue factor levels were consistently greater than those of non-DIC patients' [30,32]. The findings imply that in post-trauma DIC [30], there is widespread activation of the intrinsic coagulation system. Post-trauma DIC patients were reported to have significant changes in three important physiological anticoagulants: protein C, tissue factor pathway inhibitor, and antithrombin [30] Gando et al. [32] discovered that in post-trauma individuals with DIC, the typical tissue factor pathway inhibitor is

insufficient in blocking an activated tissue factor-dependent pathway. Additionally, they demonstrated that protein C activity and antigen levels in trauma patients with complicated DIC were much lower than in patients without DIC [33]. Owings and Gosselin [34] demonstrated that trauma patients also had considerably lower levels of antithrombin.

Natural Anticoagulant as Modulators of the Inflammatory Response

Natural anticoagulants have the ability to lessen the coagulant reaction, lessen DIC clinical symptoms, and, in certain situations, increase sepsis survival [35]. According to experimental data, decreased inflammatory responses could be the reason for the mortality decrease rather than the inhibition of coagulation per se [35]. Studies have demonstrated that various activated coagulation factors, including thrombin, factor VI-Ia, and factor Xa, can trigger cells to produce cytokines, which may be the direct cause of the reduced inflammatory response [63]. Nevertheless, even while tissue factor pathway inhibitors, protein C, and antithrombin [64–66] prevented DIC and death, In lethal primate models of sepsis, native anticoagulant therapies with heparin [67] and active site-inhibited factor Xa [68] likewise effectively blocked the activation of coagulation, but they had no effect on lethality. Therefore, it seems that the natural coagulation inhibitors' control of the inflammatory response is related to their other, non-coagulant functions [35]. Antithrombin possesses direct anti-inflammatory properties, independent of coagulation factors through an unclear mechanism. Moreover, research indicates that the tissue factor pathway inhibitor suppresses factor VI-Ia, which can cause proinflammatory alterations in mononuclear cells.

Fibrinolysis and Fibrin Degradation Products

Many studies show that at the moment of greatest activation of coagulation in DIC [1], the fibrinolytic system is mainly repressed. This reluctance is brought on by a persistent rise in the plasma concentration of plasminogen activator inhibitor 1, the primary fibrinolytic system inhibitor [70,71]. Clinical investigations have established that plasminogen activator inhibitor type 1 is the mediator of the suppression of fibrinolysis. They have also demonstrated that, despite the presence of fibrinolytic activity in response to fibrin formation, this activity is not high enough to offset systemic deposition [1,12,72, 73].

Research using experimental models of sepsis, which is the most prevalent cause of deep vein thrombosis (DIC), has proposed the idea of a procoagulant condition, which is defined by thrombin production that is higher than plasmin [74]. Numerous investigations have demonstrated that sepsis patients have activated the fibrinolytic system, as indicated by elevated plasmin-a2-and plasmin complex levels [75,76]. Comparable elevations of similar complexes have been noted in DIC [77,78] that are unrelated to Sep-Si. However, due to a more noticeable general rise in thrombin-antithrombin complexes, the majority of these patients are in a procoagulant state. Furthermore, most patients have low levels of plasminogen and a2-antitplasmin, which somewhat correlate with result [35]. But it's still unclear if this is merely a result of decreased synthesis or consumption due to a negative phase behavior. These levels have been repeatedly shown to be correlated with outcome in patients with DIC who have causes other than sepsis [80, 81]. It's interesting to note that some research has indicated that administering tissue-type plasminogen activator to animals suffering from inflammatory conditions can improve certain signs of organ failure and reduce inflammation. This suggests that increasing fibrinolysis may help treat multiple organ failure [74]. Fibrinogen is broken down by thrombin into fibrin monomer, which quickly polymerizes to form a clot [83]. Tiny quantities can circulate in plasma as soluble fibrin, which can comprise fibrinogen and varying degrees of cross-linking [83]. Its composition can be complicated.

A heterogeneous collection of degradation products reactive in D-dimer assays is formed by plasmic breakdown of cross-linked fibrin, and their levels indicate the extent of fibrin formation and lysis [83]. In experimental animal

models of DIC, significant increases of the products of fibrinogen breakdown are consistently observed. D-dimer is raised early and stays high in human models of DIC brought on by endotoxin injection, indicating the lysis of microvascular disseminated intravascular coagulation fibrin deposits [83]. For the diagnosis of DIC, elevated levels of D-dimer and soluble fibrin are highly sensitive, and a normal level has a high negative correlation is the predicted value. Additionally, D-dimer tests or serial monitoring of soluble fibrin may be useful in assessing the therapeutic response [83]. Their sensitivities range from roughly 90 to 100% [84-88], depending on the assay and the level selected to distinguish between normal and abnormal.

As a result, an increased amount of soluble fibrin or fibrin breakdown product should be present in all or almost all DIC patients. Because mechanisms other than DIC may generate increases, fibrinogen degradation products, D-dimer, and soluble fibrin tests have higher sensitivity than specificity [83]. For example, hepatic illness and renal insufficiency can both result in increased fibrinogen breakdown. For example, elevated levels of D-dimer and fibrinogen degradation product can result from both renal insufficiency and liver disease [89,80]. Because of this, it is always best to utilize these assays in conjunction with other markers [83] rather than using them alone.

Clinical Picture

Individuals with deep vein thrombosis (DIC) may have clinically less obvious microvascular thrombosis or develop thromboembolic illness mostly manifests as a dysfunction of various organs [8,91]. This means that DIC should be considered one of the causes of organ failure, although other theories contend that DIC is only a symptom of organ failure (failure of the microvasculature, which includes dysfunctional endothelial cells). Stimulated blood cells, and thus an active coagulation system) [94]. In actuality, it's possible that both mechanisms are involved. On the other hand, significant bleeding could be the primary symptom. Patients with DIC may experience simultaneous thrombosis and hemorrhage, which does not assist a clinician in selecting the most appropriate course of treatment [92]. In actuality, bleeding and thrombosis can happen in different places and to differing degrees. The thrombotic spectrum includes large intravascular deposition of fibrin that can impair circulation to laboratory evidence of hypercoagulability without significance [92]. In a similar vein, bleeding can range in severity from minimal blood loss that occurs only after an injury to enormous, spontaneous, and potentially fatal bleeding [92]. Infection [92] is the most common underlying cause of DIC in most cases. Thirty to fifty percent of patients with gram-negative sepsis may experience clinically overt DIC [10–12]. Contrary to popular assumption, patients with gram-positive sepsis appear to have clinically overt DIC just as frequently as those with gram-negative sepsis [13].

A number of processes, such as physical force, burns, or heat stroke, can generate polytrauma, which can lead to DIC. Hemolysis, phospholipid release, endothelial activation, and acidosis due to hypoperfusion [92] are the consequences of hemolysis. Although almost all patients with advanced malignant illness have enough evidence for a procoagulant condition, the frequency of overt DIC appears to be substantially lower [93]. The literature does not provide a precise incidence of DIC in patients with solid tumors, but it can be identified in 15–20% of patients presenting with leukemia [92,94].

Local stimulation of coagulation may be caused by vascular illnesses such as big hemangiomas (Kasabach-Merritt syndrome) or huge aortic aneurysms [14,15,95]. Additionally, hemangiomas of the liver and spleen, hemangioendotheliosarcoma, Osler's disease, and Klippel-Trenaunay syndrome have all been linked to signs of DIC [96–100]. A tiny percentage of patients with aneurysms in major vessels, such the aorta, may also develop DIC. A 25% incidence of clinically significant DIC has been observed in patients with massive hemangiomas [92]; however, a recent analysis of individuals with more frequent aortic aneurysms demonstrated an incidence of systemic activation of coagulation in just 1% of cases [15].

The most prevalent obstetric disorder is pre-eclampsia, which is linked to blood coagulation activation and, in severe situations, macroscopic fibrin deposits in multiple organs [101–102]. Placental abruption and amniotic fluid emboli [103] may result in acute DIC. Within four hours of the insult, women who survive severe amniotic fluid emboli are at a 50% or higher chance of developing diabetic ketoacidosis (DIC) [104].

Diagnosis

The International Society of Thrombosis and Hemostasis' Scientific Standardization Committee proposed that DIC be defined as an acquired syndrome that is characterized by intravascular activation of coagulation and loss of localization resulting from various causes. The harm it causes can start with the microvasculature and lead to organ dysfunction if it is bad enough [105].

As of right now, there isn't a single laboratory test or set of assays that is sensitive and specific enough to provide a conclusive diagnosis of DIC. Nonetheless, the majority of the time, a combination of laboratory and underlying illness results can be used to make an accurate diagnosis [106]. Numerous assays have been developed to detect the generation of thrombin (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 plas-min-antiplasmin complexes), and the resulting end products of its activity (e.g., fibrinopeptide A, soluble fibrin) [107] as a result of the recognition of the pivotal role played by thrombin in the pathophysiological process of DIC. Thrombin-antithrombin complex, F1 + 2, D-dimer, soluble fibrin, and activated protein C protein C inhibitor complex [108] are examples of sensitive indicators.

A platelet count, measurements of global clotting times (pro-thrombin time [PT] and activated partial thromboplastin time (aPTT), measurements of antithrombin III and/or 1 or 2 clotting factors, and a test for fibrin degradation products can all be used to diagnose DIC in a routine setting1. In clinical practice, the disorder can be diagnosed based on the following findings: low levels of coagulation inhibitors like antithrombin III [1], prolongation of clotting times like the PT and aPTT, elevated INR, presence of fibrin-degradation products in plasma, 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. It should be noted that in most cases, multiple coagulation tests are more beneficial in diagnosing DIC [106] than are single laboratory results. An unusual clotting profile has recently been reported, as determined by variations in light transmittance on the aPTT or PT [109,110]. With a sensitivity and specificity of more than 90%, this unusual waveform has been demonstrated in prospective trials to be a reliable, quick, and easy way to identify DIC. It also happens independently of clotting time prolongation [107,111]. Additionally, it has been described as a pre-DIC, or early predictor of imminent DIC, with implications for monitoring and prognosis in the critical care situation.

For the purpose of diagnosing DIC [112], the Japanese Ministry of Health and Welfare has created a scoring system that includes laboratory testing. An accumulation of

A score of seven or higher indicates DIC. A score of five or more is consistent with DIC, while a value of less than five may be suggestive of non-overt DIC [106], albeit it is not conclusive.

Plasma and Platelets

The risk of bleeding increases in patients with DIC who consume coagulation factors and platelets. The clinical state of the patient directs plasma or platelet concentrate treatment, which shouldn't be started based only on test results [5]. It has been demonstrated that patients requiring an invasive surgery but with poor laboratory values can benefit from therapy with plasma and platelets [93,113]. Patients who are not bleeding and who are not at high risk of bleeding should not receive platelets or plasma as a preventative measure, according to the available data1.

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 (not affirmative) for non-overt DIC; repeat next 1-2 days
It could be necessary to use significant amounts of plasma—up to six units per 24 hours—to adequately cure the coagulation defect1. This requirement may be met by using coagulation factors concentrates, although individuals with DIC5 may be especially vulnerable to their potentially hazardous residues of activated coagulation factors. Cryoprecipitate is also used as replacement therapy; it contains fibrinogen in addition to factor VIII, von Willebrand factor, factor XIII, and fibronectin. However, controlled trials have not supported its use [5].

Anticoagulants

In patients with DIC, thrombolysis should theoretically be beneficial. In fact, Heparin can partially limit the activation of coagulation in situations related to sepsis or other reasons, according to experimental studies [1]. To completely eliminate the risk of venous thromboembolism, adequate prophylaxis is also required1. Since 1959 [114], heparin has been used to treat diabetic ulcer disease. According to research on animals, this medication can prevent experimental septicemia by blocking the coagulation process, but it has no effect on mortality [115,116]. Heparin has not been found to be helpful in controlled clinical trials, but it has been in small, uncontrolled investigations including patients with DIC [117,118].
Clinical investigations have not demonstrated that therapy with heparin significantly increased the risk of bleeding, despite disagreements regarding the safety of heparin in patients with DIC who are prone to bleeding1. All things considered, there is no evidence to support the routine use of heparin as therapy in patients with DIC [5], but it is likely helpful in individuals who have severe fibrin deposition, such as in cases of acral ischemia or purpura fulminans, or clinically obvious thromboembolism [1].

Heparin with Low Molecular Weight

Heparin with a low molecular weight has the same antithrombotic capability as unfractioned heparin, but at a lower risk of bleeding.Rabbits have been shown to respond well to treatment for DIC [119]. Two small, uncontrolled human investigations that claimed successful outcomes also included [120,121]. Furthermore, a multicenter, double-blind, randomized trial [122] examined the efficacy of dalteparine sodium in the treatment of DIC. In this trial, dalteparin sodium outperformed unfractionated heparin in terms of reducing bleeding symptoms and raising the subjective score for organic symptoms. Therefore, based on this study, it may be hypothesized that while treating DIC [5], low molecular weight heparin has less bleeding problems than unfractioned heparin.

Hirudins

In animal experiments, recombinant hirudin showed promise in the treatment of diabetic foot ulcers (DIC) [123–125]. Nevertheless, there isn't a single randomized controlled study on hirudin use in DIC patients. Its usage in patients with DIC [5] may be restricted due to the elevated risk of bleeding.

Coagulation Inhibitors

Low plasma levels of antithrombin III, a significant coagulation inhibitor, are linked to a higher death rate [40]. When this inhibitor was given to animals at supraphysiologic dosages, sepsis-related mortality was decreased [126]. DIC and occasionally organ function have improved in a number of controlled trials, the majority of which involved sepsis patients [43–45]. The trials' meta-analyses revealed a drop in mortality from 56% to 44% [1].

The investigations conclude that antithrombin III can help DIC, while it is less clear if this will have a positive effect on clinical outcomes [5]. The pathogenesis of diabetic eye disease (DIC) may be considerably influenced by the depression of the protein C system. Consequently, supplementing with activated protein C may be advantageous4. Activated protein C has been demonstrated to be useful in lowering mortality and organ failure in experimental sepsis studies [66]. A large-scale randomized controlled trial shown to be clinically effective in treating severe sepsis [55]. Activated protein C group mortality was 24.7%, while placebo group mortality was 30.8%. Subsequent research verified that activated protein C can restore normal coagulation activity in cases of severe sepsis [127]. A prospective trial involving septic patients with relatively moderate illness severity did not demonstrate any advantage of activated protein C [128]; however, activated protein C appears to be more effective in greater disease severity groups [4]. Inhibiting tissue factor's activity may be useful in the treatment of DIC [5] because it is essential to the start of coagulation during DIC.

Recombinant tissue factor pathway inhibitor was infused immediately after endotoxin injection in an animal study [129], and this greatly reduced the consumption of platelets and coagulation factors. Promising outcomes were observed in phase II clinical trials with recombinant tissue factor pathway inhibitor in sepsis patients; however, a phase III trial failed to demonstrate an overall survival improvement in patients treated with tissue factor pathway inhibitor [130–131].

Conclusion. The pathogenesis of Disseminated Intravascular Coagulation (DIC) is a complex interplay of systemic activation of coagulation pathways, widespread formation of microthrombi, consumption of clotting factors and platelets, and concurrent activation of fibrinolysis. Various underlying conditions, such as sepsis, trauma, or obstetric complications, can trigger this dysregulated response, leading to a cascade of events that disrupt the delicate balance between coagulation and fibrinolysis. The resulting clinical manifestations underscore the critical importance of timely recognition and management to mitigate the potentially life-threatening consequences of DIC.

References

1. LEVI M, TEN CATE H. Disseminated intravascular coagulation. N Engl J Med 1999; 341: 586-592.
2. LANDOIS. Transfusion des Blutes. Leipzig, 1875.
3. TEN CATE H. Pathophysiology of disseminated intravascular coagulation in sepsis. Crit Care Med 2000; 28: S9-S11.
4. LEVI M. Disseminated intravascular coagulation.Crit Care Med 2007; 35: 2191-2195.
5. DE JONGE E, LEVI M, STOUTENBEEK CP, VAN DEVENTER SJH. Current drug treatment strategies for disseminated intravascular coagulation. Drugs 1998;55: 767-777.
6. WADA H. Disseminated intravascular coagulation.Clin Chim Acta 2004; 344: 13-21.
7. TEN CATE H, TIMMERMAN JJ, LEVI M. The pathophysiology of disseminated intravascular coagulation. Thromb Haemost 1999; 82: 713-717.
8. LEVI M, DE JONGE E, VAN DER POLL T, TEN CATE H.Disseminated intravascular coagulation. Thromb Haemost 1999; 82: 695-705.
9. WADA H, NAGANO T, TOMEOKU M, KUTO M, KARITANIY, DEGUCHI K, et al. Coagulant and fibrinolytic activities in the leukemic cell lysates. Thromb Res1982; 30: 315-322.
10. THIJS LG, DE BOER JP, DE GROOT MCM, HACK CE. Coagulation disorders in septic shock. Intensive Care Med 1993; 19: Suppl 1: S8-S15.
11. BAGLIN T. Disseminated intravascular coagulation:diagnosis and treatment. Br Med J 1996; 312: 683-687.
12. GANDO S, KAMEUE T, NANZAKI S, NAKANISHI Y. Disseminated intravascular coagulation is a frequent complication of systemic inflammatory

response syndrome. Thromb Haemost 1996; 75: 224-228.
13. BONE RC. Gram-positive organisms and sepsis.Arch Intern Med 1994; 154: 26-34.
14. SZLACHETKA DM. Kasabach-Merritt syndrome: a case review. Neonatal Netw 1998; 17: 7-15. [Erratum, Neonatal Netw 1998; 17: 21].
15. ABOULAFIA DM, ABOULAFIA ED. Aortic aneurysm-induced disseminated intravascular coagulation. Ann Vasc Surg 1996; 10: 396-405.
16. KAZMERS A, JACOBS L, PERKINS A, LINDENAUER SM,BATES E. Abdominal aortic aneurysm repair in Veterans Affairs Medical Centers. J Vasc Surg 1996; 23: 191-200.
17. RUGGENENTI P, LUTZ J, REMUZZI G. Pathogenesis and treatment of thrombotic microangiopathy. Kidney Int 1997; 58: S97-S101.
18. VAN DER POLL T, BÜLLER HR, TEN CATE H, WORTEL CH,BAUER KA, VAN DEVENTER SJ, HACK CE, SAUERWEIN HP,ROSENBERG RD, TEN CATE JW. Activation of coagulation after administration of tumor necrosis factor to normal subjects. N Engl J Med 1990; 322:1622-1627.
19. LEVI M, VAN DER POLL T, TEN CATE H, VAN DEVENTERSJH. The cytokinemediated imbalance between coagulant and anticoagulant mechanisms in sepsis and endotoxemia. Eur J Clin Invest 1997; 27:3-9.
20. BARBUI T, FALANGA A. Disseminated intravascular coagulation in acute leukaemia. Semim Thromb Hemost 2001; 27: 593-604.
21. RICKLES FR, LEVINE MN, EDWARDS RL. Hemostatic alterations in cancer patients. Cancer Met Rev 1992; 11: 237-248.
22. FALANGA A, BARBUI T, RICKLES FR, LEVINE MN. Guidelines for clotting studies in cancer patients. Thromb Haemost 1993; 70: 343-350.
23. FALANGA A, OFOSU FA, DELAINI F, OLDANI E, DEWAR LLUI L, BARBUI T. The hypercoagulable state in cancer: Evidence for impaired thrombin inhibition.Blood Coagul Fibrinolysis 1994; 5: S19-S23.
24. FALANGA A. Mechanisms for hypercoagulation in malignancy and during chemotherapy. Haemostasis 1998; 28(Suppl 3): 50-60.
25. TALLMAN MS, KWAAN HC. Reassessing the hemostatic disorder associated with acute promyelocytic leukemia. Blood 1992; 79: 543-553.
26. BAUER KA, ROSENBERG RD. Thrombin generation in acute promyelocytic leukaemia. Blood 1984; 64:791-796.
27. BOOTH NA, BENNETT B. Plasmin-alpha-2-antiplasmin complexes in bleeding disorders characterized by primary or secondary fibrinolysis. Br J Haematol 1984; 56: 545-556.
28. REDDY VB, KOWAL-VERN A, HOPPENSTEADT DA, KUMAR A, WALENGA JM, FAREED J, SCHUMACHER HR.Global and hemostatic markers in acute myeloid leukemia. Am J Clin Pathol 1990; 94: 397-403.
29. SPEISER W, PABINGER-FASCHING I, KYRLE PA, KAPIOTIS S, KOTTAS-HELDENBERG A, BETTELHEIM P, LECHNER K. Hemostatic and fibrinolytic parameters in patients with acute myeloid leukemia: Activation of blood coagulation, fibrinolysis and unspecific proteolysis. Blut 1990; 61: 298-302.
30. GANDO S. Disseminated intravascular coagulation in trauma patients. Semin Thromb Hemost 2001; 27: 585-592.
31. LEVI M, TEN CATE H, VAN DER POLL T, VAN DEVENTER SJH. Pathogenesis of disseminated intravascular coagulation in sepsis. JAMA 1993; 270: 975-979.
32. GANDO S, NANZAKI S, MORIMOTO Y, ISHITANI T, KEMMOTSU O. Tissue factor pathway inhibitor response does not correlate with tissue-factor induced DIC and MODS in trauma patients. Crit Care Med 2001; 24: 262-266.
33. GANDO S. Serial studies of protein C in trauma patients. Jpn J Thromb Hemost 1996; 7: 312-318.

34. OWINGS JT, GOSSELIN R. Acquired antithrombin deficiency following severe traumatic injury: Rationale for study of antithrombin supplementation.Semin Thromb Hemost 1997; 23(Suppl 1): 17-24.
35. DE JONGE E, VAN DER POLL T, KESECIOGLU J, LEVI M.Anticoagulant factor concentrates in disseminated intravascular coagulation: rationale for use and clinical experience. Semin Thromb Hemost 2001; 27: 667-674.
36. RAO LV, NORDFANG O, HOANG AD, PENDURTHI UR.Mechanism of antithrombin III inhibition of factor VIIa/tissue factor activity on cell surfaces. Comparison with tissue factor pathway inhibitor/factor Xa-induced inhibition of factor VIIa/tissue factor activity. Blood 1995; 85: 121-129.
37. Babanazarov, U. T., & Barnoyev, S. S. (2023). Clinical Characteristics of Patients with Chronic Diffuse Liver Disease Against the Background of Covid-19. Genius Repository, 26, 49-55.
38. BÜLLER HR, TEN CATE JW. Acquired antithrombin III deficiency: Laboratory diagnosis, incidence, clinical implications, and treatment with antithrombin III concentrate. Am J Med 1989; 87: 44S-48S.
39. SEITZ R,WOLF M, EGBRING R, HAVEMANN K. The disturbance of hemostasis in septic shock: Role of neutrophil elastase and thrombin, effects of antithrombin III and plasma substitution. Eur J Haematol 1989; 43: 22-28.
40. FOURRIER F, CHOPIN C, GOUDEMAND J, HENDRYCX S,CARON C, RIME A, MAREY A, LESTAVEL P. Septic shock,multiple organ failure, and disseminated intravascular coagulation. Compared patterns of antithrombin III, protein C, and protein S deficiencies. Chest 1992; 101: 816-823.
41. BLAUHUT B, KRAMAR H, VINAZZER H, BERGMANN H.Substitution of antithrombin III in shock and DIC: A randomized study. Thromb Res 1985; 39: 81-89.
42. VINAZZER H. Therapeutic use of antithrombin III in shock and disseminated intravascular coagulation. Semin Thromb Hemost 1989; 15: 347-352.
43. FOURRIER F, CHOPIN C, HUART JJ, RUNGE I, CARON C,GOUDEMAND J. Double-blind, placebo-controlled trial of antithrombin III concentrates in septic shock with disseminated intravascular coagulation. Chest 1993; 104: 882-888.
44. BAUDO F, CAIMI TM, DE CATALDO F, RAVIZZA A, ARLATI S,CASELLA G, CARUGO D, PALARETI G, LEGNANI C, RIDOLFIL, ROSSI R, D'ANGELO A, CRIPPA L, GIUDICI D, GALLIOLIG, WOLFLER A, CALORI G. Antithrombin III (ATIII) replacement therapy in patients with sepsis and/or postsurgical complications: A controlled double-blind, randomized, multicenter study. Intens Care Med 1998; 24: 336-342.
45. EISELE B, LAMY M, THIJS LG, KEINECKE HO, SCHUSTER HP, MATTHIAS FR, FOURRIER F, HEINRICHS H, DELVOS U.Antithrombin III in patients with severe sepsis. A randomized, placebo-controlled, double-blind multicenter trial plus a meta-analysis on all randomized, placebo-controlled, double-blind trials with antithrombin III in severe sepsis. Intens Care Med 1998; 24: 663-672.
46. INTHORN D, HOFFMANN JN, HARTL WH, MUHLBAYER D, JOCHUM M. Effect of antithrombin III supplementation on inflammatory response in patients with severe sepsis. Shock 1998; 10: 90-96.
47. INTHORN D, HOFFMANN JN, HARTL WH, MUHLBAYER D, JOCHUM M. Antithrombin III supplementation in severe sepsis: Beneficial effects on organ dysfunction. Shock 1997; 8: 328-334.
48. MAKI M,TERAO T, IKENOUE T, TAKEMURA T, SEKIBA K, SHIRAKAWA K, SOMA H. Clinical evaluation of antithrombin III concentrate (BI 6.013) for disseminated intravascular

coagulation in obstetrics. Well-controlled multicenter trial. Gynecol Obstet Invest 1987; 23: 230-240.
49. NAWROTH PP, HANDLEY DA, ESMON CT, STERN DM. Interleukin 1 induces endothelial cell procoagulant while suppressing cell-surface anticoagulant activity. Proc Natl Acad Sci USA 1986; 83: 3460-3464.
50. NAWROTH PP, STERN DM. Modulation of endothelial cell hemostatic properties by tumor necrosis factor. J Exp Med 1986; 163: 740-745.
51. FUKUDOME K, ESMON CT. Identification, cloning, and regulation of a novel endothelial cell protein C/activated protein C receptor. J Biol Chem 1994; 269: 26486-26491.
52. BOEHME MW, DENG Y, RAETH U, BIERHAUS A, ZIEGLER R, STREMMEL W, NAWROTH PP. Release of thrombomodulin from endothelial cells by concerted action of TNFalpha and neutrophils: In vivo and in vitro studies. Immunology 1996; 87: 134-140.
53. SLUNGAARD A, VERCELLOTTI GM,TRAN T, GLEICH GJ, KEY NS. Eosinophil cationic granule proteins impair thrombomodulin function. A potential mechanism for thromboembolism in hypereosinophilic heart disease. J Clin Invest 1993; 91: 1721-1730.
54. HESSELVIK JF,MALM J, DAHLBÄCK B, BLOMBÄCK M. Protein C, protein S and C4b-binding protein in severe infection and septic shock. Thromb Haemost 1991; 65: 126-129.
55. BERNARD GR, VINCENT JL, LATERRE PF, LAROSA SP,DHAINAUT JF, LOPEZ-RODRIGUEZ A, STEINGRUB JS, GARBER GE, HELTERBRAND JD, ELY EW, FISHER CJ Jr. Recombinant human Protein C worldwide evaluation in severe sepsis (PROWESS) study group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001; 344: 699-709.
56. Turobkulovich, B. U., & Tuymurodovich, K. M. (2022). Coronavirus Infection-A Trigger Factor in Liver Damage. Eurasian Research Bulletin, 15, 52-58.
57. CAMERER E, KOLSTO AB, PRYDZ H. Cell biology of tissue factor, the principal initiator of blood coagulation. Thromb Res 1996; 81: 1-41.
58. MANN KG. Biochemistry and physiology of blood coagulation. Thromb Haemost 1999; 82: 165-174.
59. MORRISSEY JH, FAKHRAI H, EDGINGTON TS. Molecular cloning of the cDNA for tissue factor, the cellular receptor for the initiation of the coagulation protease cascade. Cell 1987; 50: 129-135.
60. CREASEY AA. New potential therapeutic modalities:Tissue factor pathway inhibitor. Sepsis 1999; 3: 173-182.
61. DE JONGE E, DEKKERS PE, CREASEY AA, HACK CE, PAULSON SK, KARIM A, KESECIOGLU J, LEVI M, VAN DEVENTER SJ, VAN DER POLL T. Tissue factor pathway inhibitor dose-dependently inhibits coagulation activation without influencing the fibrinolytic and cytokine response during human endotoxemia. Blood 2000;95: 1124-1129.
62. KEMME MJ, BURGGRAAF J, SCHOEMAKER RC, PAULSON S, KARIM A, LENTJES EG, CHILDS A, BRAECKMAN RA, COHEN AF. The influence of reduced liver blood flow on the pharmacokinetics and pharmacodynamics of recombinant tissue factor pathway inhibitor.Clin Pharmacol Ther 2000; 67: 504 511.
63. ESMON CT. Introduction: Are natural anticoagulants candidates for modulating the inflammatory response to endotoxin? Blood 2000; 95: 1113-1116.
64. CREASEY AA, CHANG AC, FEIGEN L, WÜN TC, TAYLOR FB JR, HINSHAW LB. Tissue factor pathway inhibitor reduces mortality from Escherichia coli septic shock. J Clin Invest 1993; 91: 2850-2860.
65. TAYLOR FBJ, EMERSON TEJ, JORDAN R, CHANG AK, BLICK, KE. Antithrombin-III prevents the lethal effects of Escherichia coli infusion in baboons. Circulatory Shock 1988; 26: 227-235.

66. 66) TAYLOR FB, CHANG A, ESMON CT, D'ANGELO A,VIGANO-D'ANGELO S, BLICK KE. Protein C prevents the coagulopathic and lethal effects of Escherichia coli infusion in the baboon. J Clin Invest 1987; 79: 918-925.
67. Babanazarov, U. T., & Qayimov, M. T. (2023). Epidemiology, Etiology, Clinical Description, and Prevention of Postoperative Cognitive Dysfunction. Eurasian Research Bulletin, 19, 38-46.
68. TAYLOR FBJ, CHANG AC, PEER GT, et al. DEGR-factor Xa blocks disseminated intravascular coagulation initiated by Escherichia coli without preventing shock or organ damage. Blood 1991; 78: 364-368.
69. CUNNINGHAM MA, ROMAS P, HUTCHINSON P,HOLDSWORTH SR, TIPPING PG. Tissue factor and factor VIIa receptor/ligand interactions induce proinflammatory effects in macrophages. Blood 1999; 94: 3413-3420.
70. LEVI M, TEN CATE H, BAUER KA, VAN DER POLL T, EDGINGTON TS, BÜLLER HR, VAN DEVENTER SJ, HACK CETEN CATE JW, ROSENBERG RD. Inhibition of endotoxin-induced activation of coagulation and fibrinolysis by pentoxifylline or by a monoclonal anti-tissue factor antibody in chimpanzees. J Clin Invest 1994; 93: 114-120.
71. SUFFREDINI AF, HARPEL PC, PARRILLO JE. Promotion and subsequent inhibition of plasminogen activator after administration of intravenous endotoxin to normal subjects. N Engl J Med 1989; 320: 1165-1172.
72. GANDO S, NAKANISHI Y, TEDO I. Cytokines and plasminogen activator inhibitor-1 in post trauma disseminated intravascular coagulation: relationship to multiple organ dysfunction syndrome. Crit Care Med 1995; 23: 1835-1842.
73. NOSSEL HL. Relative proteolysis of the fibrinogen B beta chain by thrombin and plasmin as a determinant of thrombosis. Nature 1981; 291: 165-167.
74. HACK EC. Fibrilolysis in disseminated intravascular coagulation. Semin Thromb Hemost 2001; 27: 633-638.
75. KARIO K, MATSUO T, KODAMA K, MATSUO M, YAMAMOTOK, KOBAYASHI H. Imbalance between thrombin and plasmin activity in disseminated intravascular coagulation. Assessment by the thrombin-antithrombin-III complex/plasmin-alpha-2-antiplasmin complex ratio. Haemostasis 1992; 22: 179-186.
76. TAKAHASHI H, TATEWAKI W, WADA K, HANANO M, SHIBATA A. Thrombin vs. plasmin generation in disseminated intravascular coagulation associated with various underlying disorders [see comments]. AmJ Hematol 1990; 33: 90-95.
77. OKAMOTO K, TAKAKI A, TAKEDA S, KATOH H, OHSATO K. Coagulopathy in disseminated intravascular coagulation due to abdominal sepsis: Determination of prothrombin fragment 1 + 2 and other markers. Haemostasis 1992; 22: 17-24.
78. ASAKURA H, JOKAJI H, SAITO M, UOTANI C, KUMABASHIRI I, MORISHITA E, YAMAZAKI M, AOSHIMA K, MATSUDA T.Study of the balance between coagulation andfibrinolysis in disseminated intravascular coagulation using molecular markers. Blood Coagul Fibrin 1994; 5: 829-832.
79. NIESSEN RW, LAMPING RJ, JANSEN PM, PRINS MH, PETERS M, TAYLOR FB JR, DE VIJLDER JJ, TEN CATE JW,HACK CE, STURK A. Antithrombin acts as a negative acute phase protein as established with studies on HepG2 cells and in baboons. Thromb Haemost 1997; 78: 1088-1092.
80. MESTERS RM, FLORKE N, OSTERMANN H, KIENAST J. Increase of plasminogen activator inhibitor levels predicts outcome of leukocytopenic patients with sepsis. Thromb Haemost 1996; 75: 902-907.
81. PRALONG G, CALANDRA T, GLAUSER MP, SCHELLEKENS J,VERHOEF J, BACHMANN F, KRUITHOF EK.

Plasminogen activator inhibitor 1: a new prognostic marker in septic shock. Thromb Haemost 1989; 61: 459-462.
82. BRANDTZAEG P, JOO GB, BRUSLETTO B, KIERULF P.Plasminogen activator inhibitor 1 and 2, alpha-2- antiplasmin, plasminogen, and endotoxin levels in systemic meningococcal disease. Thromb Res 1990; 57: 271-278.
83. HORAN JT, FRANCIS CW. Fibrin degradation products, fibrin monomer and soluble fibrin in disseminated intravascular coagulation. Semin Thromb Hemost 2001; 27: 657-666.
84. YU M, NARDELLA A, LECHET L. Screening tests of disseminated intravascular coagulation: Guidelines for rapid and specific laboratory diagnosis.Crit Care Med 2000; 28: 1777-1780.
85. OKAJIMA K, UCHIBA M, MURAKAMI K, OKABE H, TAKATSUKI K. Determination of plasma soluble fibrin using a new ELISA method in patients with disseminated intravascular coagulation. Am J Hematol 1996; 51: 186-191.
86. CARR JM, MCKINNEY M, MCDONAGH J. Diagnosis of disseminated intravascular coagulation. Role of D-dimer. Am J Clin Pathol 1989; 91: 280-287.
87. BICK RL, BAKER WF. Diagnostic efficacy of the D-dimer assay in disseminated intravascular coagulation (DIC). Thromb Res 1992; 65: 785-790.
88. WADA H,WAKITA Y, NAKASE T, SHIMURA M, HIYOYAMAK, NAGAYA S, DEGUCHI H, MORI Y, KANEKO T,DEGUCHI K, FUJII J, SHIKU H. Increased plasma-soluble fibrin monomer levels in patients with disseminated intravascular coagulation. Am J Hematol 1996; 51: 255-260.
89. LANE DA, IRELAND H, KNIGHT I, WOLFF S, KYLE P, CURTIS JR. The significance of fibrinogen derivatives in plasma in human renal failure. Br J Haematol1984; 56: 251-260.
90. VANDEWATER L, CARR JM, ARONSON D, MCDONAGH J. Analysis of elevated fibrinogen degradation product levels in patients with liver disease.Blood 1986; 67: 1468-1473.
91. MARDER VJ, FEINSTEIN D, FRANCIS C, COLMAN RW. Consumptive thrombo-hemorrhagic disorders. In: Colman RW, Hirsh J, Marder VJ, Salzman E,eds. Hemostasis and Thrombosis: Basic Principles and Clinical Practice, 3rd ed. Philadelphia: Lippincott; 1994: pp. 1023-1063.
92. LEVI M, DE JONGE E, VAN DER POLL, TEN GATE H. Advantages in the understanding of the pathogenic pathways of disseminated intravascular coagulation result in more insight in the clinical picture and better management strategies. Semin Thromb Hem 2001; 27: 569-575.
93. COLMAN RW, RUBIN RN. Disseminated intravascular coagulation due to malignancy. Semin Oncol 1990; 17: 172-186.
94. SARRIS AH, KEMPIN S, BERMAN E, MICHAELI J, LITTLE C, ANDREEFF M, GEE T, STRAUS D, GANSBACHER B, FILIPPAD. High incidence of disseminated intravascular coagulation during remission induction of adult patients with acute lymphoblastic leukemia. Blood 1992; 79: 1305-1310.
95. GIBNEY EJ, BOUCHIER-HAYES D. Coagulopathy and abdominal aortic aneurysm. Eur J Vasc Surg 1990; 4: 557-562.
96. EL-DESSOUKY M, AZMY AF, RAINE PA, YOUNG DG. Kasabach-Merritt syndrome. J Pediatr Surg 1988; 23: 109-111.
97. D'AMICO JA, HOFFMAN GC, DYMENT PG. Klippel-Trenaunay syndrome associated with chronic disseminated intravascular coagulation and massive osteolysis. Cleve Clin Q 1977; 44: 181-188.
98. POON MC, KLOIBER R, BIRDSELL DC. Epsilon-aminocaproic acid in the reversal of consumptive coagulopathy with platelet sequestration in avascular malformation of Klippel-Trenaunay syndrome. Am J Med 1989; 87: 211-213.
99. ALPERT LI, BENISCH B. Hemangioendothelioma of the liver

associated with microangiopathic hemolytic anemia. Report of four cases. Am J Med 1970; 48: 624-628.
100. BICK RL. Hereditary hemorrhagic telangiectasia and disseminated intravascular coagulation. A new clinical syndrome. Ann N Y Acad Sci 1981; 370: 851-854.
101. DE BOER K, TEN CATE JW, STURK A, BORM JJ, TREFFERSPE. Enhanced thrombin generation in normal and hypertensive pregnancy. Am J Obstet Gynecol 1989; 160: 95-100.
102. WEINER CP. Preeclampsia-eclampsia syndrome and coagulation. Clin Perinatol 1991; 18: 713-726.
103. WEINER CP. The obstetric patient and disseminated intravascular coagulation. Clin Perinatol 1986; 13: 705-717.
104. MCDOUGALL RJ, DUKE GJ. Amniotic fluid embolism syndrome. Case report and review. Anaesthesia Intens Care 1995; 23: 735-740.
105. TAYLOR JR FB, TOH CH, HOOTS WK, WADA H, LEVIM. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation—on behalf of the Scientific Subcommittee on disseminated intravascular coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH).Thromb Haemost 2001; 86: 1327-1230.
106. LEVI M, DE JONGE E, MEIJERS J. The diagnosis of disseminated intravascular coagulation. Blood Rev 2002; 16: 217-223.
107. HOCK TOH C. Laboratory testing in disseminated intravascular coagulation. Semin Thromb Hemost 2001; 27: 653-656.
108. MINAMIKAWA K, WADA H, WAKITA Y, OHIWA M, TANIGAWAM, DEGUCHI K, HIRAOKA N, HUZIOKA H, NISHIOKA J,HAYASHI T. Increased activated protein C- protein C inhibitor complex levels in patients with pulmonary embolism. Thromb Haemost 1994; 71: 192-194.
109. DOWNEY C, KAZMI R, TOH CH. Novel and diagnostically applicable information from optical wave form analysis of blood coagulation in disseminated intravascular coagulation. Br J Haematol 1997; 98: 68-73.
110. TOH CH, DOWNEY C, DWYRE L. Thromboplastin sensitivity in waveform analysis. Thromb Haemost 2000; 84: 517-518.
111. DOWNEY C, KAZMI R, TOH CH. Early identification and prognostic implications in disseminated intravascular coagulation through transmittancewaveform analysis. Thromb Haemost 1998; 80: 65-69.
112. KOBAYASHI N, MAEKAWA T, TAKADA M, TANAKA H, GONMORI H. Criteria for diagnosis of DIC based on analysis of clinical and laboratory findings in 345 DIC patients collected by the Research Committee on DIC in Japan. Bibl Haematol 1983; 49: 265-275.
113. FEINSTEIN DI. Treatment of disseminated intravascular coagulation. Semin Thromb Hemost1988;14: 351-362.
114. LITTLE JR. Purpura fulminans treated successfully with anticoagulation: report of a case. JAMA 1959; 169: 36-40.
115. GASKINS JR RA, DALLDORF FG. Experimental meningococcal septicemia: effect of heparin therapy. Arch Pathol Lab Med 1976; 100: 318-324.
116. CORRIGAN JR JJ, KIERNAT JF. Effect of heparin in experimental Gram-negative septicemia. J Infect Dis 1975; 131: 138-43.
117. CORRIGAN JJ JR. Heparin therapy in bacterial septicemia. J Pediatr 1977; 91: 695-700.
118. FEINSTEIN DI. Diagnosis and management of disseminated intravascular coagulation: the role of heparin therapy. Blood 1982; 60: 284-287.
119. TAKAHASHI Y, HOSAKA Y, IMADA K, ADACHI T, NIINA H,WATANABE M, MOCHIZUKI H. Human urinary soluble

thrombomodulin (MR-33) improves disseminated intravascular coagulation without affecting bleeding time in rats: comparison with low molecular weight heparin. Thromb Haemost 1997;77: 789-795.

120. AUDIBERT G, LAMBERT H, TOULEMONDE F, ALEXANDRE P,LAPREVOTE-HEULLY MC, BOLLAERT PE, BAUER P, LARCANA. Utilisation d'une héparine de bas poids moléculaire, la CY 222, dans le traitement descoagulopathies de consommation. J Mal Vasc 1987; 12 Suppl. B: 147-151.
121. GILLIS S, DANN EJ, ELDOR A. Low molecular weight heparin in the prophylaxis and treatment of disseminated intravascular coagulation in acute promyelocytic leukemia. Eur J Haematol 1995;54: 59-60.
122. SAKURAGAWA N, HASEGAWA H, MAKI M, NAKAGAWA M, NAKASHIMA M. Clinical evaluation of low-molecular-weight heparin (FR-860) on disseminated intravascular coagulation (DIC) – a multicenter cooperative double-blind trial in comparison with heparin. Thromb Res 1993; 72: 475-500.
123. FREUND M, CAZENAVE JP, COURTNEY M, DEGRYSE E, ROITSCH C, BERNAT A, DELEBASSÉE D, DEFREYN G, MAFFRAND JP. Inhibition by recombinant hirudins of experimental venous thrombosis and disseminated intravascular coagulation induced by tissue factor in rats. Thromb Haemost 1990; 63:187-192.
124. ZAWILSKA K, ZOZULINSKA M, TUROWIECKA Z, BLAHUTM, DROBNIK L, VINAZZER H. The effect of a long-acting recombinant hirudin (PEG-hirudin) on experimental disseminated intravascular coagulation (DIC) in rabbits. Thromb Res 1993; 69: 3153-3120.
125. DICKNEITE G, CZECH J. Combination of antibiotic treatment with the thrombin inhibitor recombinant hirudin for the therapy of experimental Klebsiella pneumoniae sepsis. Thromb Haemost 1994; 71: 768-772.
126. KESSLER CM, TANG Z, JACOBS HM, SZYMANSKI LM. The suprapharmacological dosing of antithrombin concentrate for Staphylococcus aureus induced disseminated intravascular coagulation inguinea pigs: substantial reduction in mortality and morbidity. Blood 1997; 89: 4393-401.
127. DE PONT AC, BAKHTIARI K, HUTTEN BA, DE JONGE E,VROOM MB, MEIJERS JC, BÜLLER HR, LEVI M. Recombinant human activated protein C resets thrombin generation in patients with severe sepsis: A case control study. Crit Care 2005; 9: R490-R497.
128. ABRAHAM E, LATERRE PF, GARG R, LEVY H, TALWAR D, TRZASKOMA BL, FRANÇOIS B, GUY JS, BRÜCKMANN M, REA-NETO A, ROSSAINT R, PERROTIN D, SABLOTZKI A, ARKINS N, UTTERBACK BG, MACIAS WL; ADMINISTRATION OF DROTRECOGIN ALFA (ACTIVATED) IN EARLY STAGE SEVERESEPSIS (ADDRESS) STUDY GROUP. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. N Engl J Med 2005; 353: 1332-1341.
129. ELSAYYED YA, NAKAGAWA K, KAMIKUBO YI, ENJYOJI KI, KATO H, SUEISHI K. Effects of recombinant human tissue factor pathway inhibitor on thrombus formation and its in vivo distribution in a rat DIC model. Am J Clin Pathol 1996; 106: 574-583.
130. ABRAHAM E, REINHART K, SVOBODA P, SEIBERT A, OLTHOFF D, DAL NOGARE A, POSTIER R, HEMPELMANNG, BUTLER T, MARTIN E, ZWINGELSTEIN C, PERCELL S, SHU V, LEIGHTON A, CREASEY AA. Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: A multicenter, randomized, placebo-controlled, single-blind, dose escalation study. Crit Care Med 2001; 29: 2081-2089.

131. ABRAHAM E, REINHART K, OPAL S, DEMEYER I, DOIG C, RODRIGUEZ AL, BEALE R, SVOBODA P, LATERRE PF, SIMON S, LIGHT B, SPAPEN H, STONE J, SEIBERT A, PECKELSEN C, DE DEYNE C, POSTIER R, PETTILÄ V, ARTIGASA, PERCELL SR, SHU V, ZWINGELSTEIN C, TOBIAS J, POOLE L, STOLZENBACH JC, CREASEY AA; OPTIMIST TRIAL STUDY GROUP. Efficacy and safety of tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis: A randomized controlled trial. JAMA 2003; 290: 238-247.