Management of DIC in the ICU: an update

Michael P. Hutchens, Per Thorborg

Abstract

Disseminated Intravascular Coagulation is not uncommon in the ICU. Presentations can vary from unexpected DVT or PE to severe generalized bleeding. This review discusses the etiology as well as the present understanding of the underlying pathophysiology in some details. This review will enable the intensivist to understand the background for the diagnosis and new innovative ways of treatment of DIC.

Keywords: Disseminated Intravascular Coagulation, DIC, Tissue Factor, TF, Activated Protein C, APC, rFVIIa

Introduction and Etiologies

Disseminated Intravascular Coagulation (DIC) is a condition that severely perturbs the delicate equilibrium between thrombosis and flow in the microcirculation. Widespread microembolization is believed to be the precursor of tissue perfusion failure, leading to Multiple System Organ Failure (MSOF) and death. This complex disorder of the coagulation system is therefore often seen as a harbinger of death, thus an understanding of the pathophysiology, diagnosis and management of DIC is fundamental in managing the critical care patient. The purpose of this article is to provide an update on the management of DIC for the intensivist.

DIC is common in ICU patients, as it is a comorbidity of many of the diagnoses, which lead to ICU admission. While DIC is not a primary disorder, it is a marker of an underlying systemic process. Presentation may vary widely – from clinically unsuspected, as in many patients with aortic aneurysms [1] to fulminant and rapidly fatal, as in trauma and sepsis patients in whom DIC increases the risk of death [2].

Key etiologies in acute DIC include sepsis, delayed shock resuscitation, trauma, certain cancers, obstetric complications, preeclampsia, burn injury, immunologic disorders, vasculitis, after certain blood products, after cardiopulmonary bypass, newborn purpura fulminans and after exposure to toxins[3]. In multiple series, 30 - 50 % of patients with gram-negative sepsis will develop DIC, as will 50 - 70% of patients with severe trauma and fat embolism, up to 15 % of patients with certain hematologic malignancies, and up to 50 % of patients with severe obstetrical complications as e.g., amniotic fluid embolism[4]. In contrast, only 7% of pre-eclamptic patients develop DIC. Immunologic disorders associated with acute DIC include TTP, HELLP syndrome, transfusion and transplant reactions. Patients with acute promyelocytic leukemia and metastatic prostate cancer are at particular risk[5, 6]. The etiology can be diverse, of patients with DIC, 27 % are neither cancer, obstetric, nor aneurysmal in origin [1]. A number of other conditions, including envenomations and recreational drug use are known to have associations with acute DIC [7] [8].

Chronic DIC etiologies include cancers (such as pancreatic cancer), aortic aneurysm and giant cavernous hemangiomas (Kasabach-Merritt syndrome), dead fetus in utero and some types of chronic infections (tuberculosis, abscess, osteomyelitis). Chronic inflammatory bowel disease (Crohn’s disease, Ulcerative colitis) can exhibit slow onset DIC. Chronic DIC can be asymptomatic or manifest in DVT and/or PE.

Pathophysiology of DIC:

DIC is a complex disorder, which may be more easily understood using a two-phase model[9]: initiation and maintenance.
Initiation

This initiation phase of DIC is essentially identical to the initiation of any nonpathologic clot. In the extrinsic pathway, vascular injury leads to the initiation of coagulation by exposing plasma (blood) to tissue factor (TF). This FVII cofactor is normally situated in the adventitia and in the cell membrane of many other cell types not in direct contact with plasma, providing a hemostatic envelope to the vasculature. The TF/FVIIa complex can activate FIX and FX locally (in the Extrinsic Tenase complex) to form small amount of thrombin, enough to activate platelets, but not to form much fibrin. Once the platelets are so activated, FX and FV (the Prothrombinase complex) will generate more thrombin and provide opportunity for thrombin feedback of its own production through FVIII, FIX and FXI (in the Intrinsic Tenase complex). This "thrombin burst" produces enough thrombin for rapid fibrin production to build a dense fibrin coating of the initial frail platelet clot (a.k.a. the primary hemostasis), more resistant to fibrinolysis. Several modulating systems making it control the speed of the above reactions, first tissue factor pathway inhibitor (TFPI) rapidly inactivates the Extrinsic tenase complex after it forms FXa. In DIC, however, this does not appear to be an effective pathway to neutralize large amounts of TF. The second modulator is antithrombin (AT, formerly also called AT-III) that inactivates formed thrombin as well as FXa, FIXa and FXIa. Heparan, the naturally appearing glucosaminoglycan, increases the speed of this pathway. The third modulating system is the protein C (PC)/protein S (PS) system itself activated by the surface-bound molecule thrombomoduline (TM) and thrombin. PC and its cofactor PS will once activated, inactivate FVas and FVIIIa. Deficiencies or abnormalities of the AT or PC/PS modulating systems as in hereditary states or by consumption in DIC, lead to prothrombotic states of varying severity. There is some data to suggest that AT, and particularly PC replacement, in DIC with low plasma levels of these control factors, respectively, improves survival.

Normal hemostasis also includes secondary fibrinolysis, that normally is initiated by tPA action on plasminogen to produce plasmin, that in turn degrades fibrin (and fibrinogen) to fibrin split products (FSP a.k.a. FDP). Plasmin activity is controlled by alpha2-antiplasmin. Plasminogen activator inhibitor (PAI-1) inactivates tPA and thereby controls the degree of fibrinolysis. Cross-linked fibrin (from a clot), when lysed by plasmin, will produce small fibrin segments known as D-dimers. So while the secondary hemostasis is to a large extent driven by thrombin, the fibrinolysis is counterbalanced by plasmin. See Figure 1[10].

Up-regulation of TF expression leading to widespread coagulation activation can likely be achieved through different pathways. Transcription of TF from chromosome 1 through mRNA is known to exist in several lines of cells, such as splenic endothelial cells, fibroblasts, monocytes and smooth muscle cells. Transcriptional control in sepsis is known to be exerted by the protein nuclear-factor kB (NFKB) (and other factors), itself induced by activated platelets[11]. In the event of trauma, this likely represents an amplification process in which the original TF exposure invokes platelet activation, and subsequently massive expression of TF. This helps explain why a local injury (such as extremity trauma or brain injury) can induce systemic DIC. In sepsis and SIRS, and other pro-inflammatory states, the IL-6 release appears to be the primary event leading to TF up-regulation. The second cytokine known to affect the coagulation balance in inflammatory states is tumor necrosis factor alpha, TNF-α, which down-regulates TM (which up-regulates coagulation), and also up-regulates PAI-1 (which down-regulates fibrinolysis) tilting the balance such that coagulation is favored and fibrinolysis is reduced.

Maintenance

The maintenance phase of DIC begins within minutes of initiation. While TF accounts for initiation of DIC in most instances, it does not appear to play a role in the maintenance phase, since TFPI does not appear to be an effective treatment in DIC. Multiple amplifications and regulatory mechanisms result in consumption of platelets, coagulation factors as well as their modulators, and impaired fibrinolysis. Since the liver synthesizes almost all coagulation factors (both pro- and anti-coagulant) at a certain speed, the point where coagulation factor levels start to drop will depend on the speed of their consumption. For the primary hemostasis, the same considerations apply to the speed of production of platelets by the bone marrow (and their clearance by the reticuloendothelial system). If the liver can keep production in pace with consumption, as in chronic DIC, the state is usually called compensated, but when consumption outpaces production (acute DIC) the state becomes decompensated. Compensated DIC is usually a prothrombotic or sometimes asymptomatic state, while decompensated DIC is characterized by diffuse bleeding.

The reasons for the decompensation are multiple. Platelets subjected to supraphysiologic activation stimuli become depleted of ATP, degranulated, and misshapen[3]. In DIC, AT levels are often low due to rapid consumption at clot sites. AT is also down regulated and degraded by neutrophils that are activated in the initiation phase[12].
Protein C and S levels are frequently depleted in DIC patients. It was in part this observation and the fact that mortality is significantly increased in patients with protein C deficiency that led to the use of activated PC (APC) as a therapy for severe sepsis[13]. It was therefore confusing to find that in this trial the actual PC levels did not correlate with the effect of APC on mortality. Larger APC trials for severe sepsis currently underway may shed more light on this. Additionally, APC has a pronounced anti-inflammatory effect which may account for some of its beneficial effect in these sepsis trials, particularly in the light of inflammatory mediator cross talk with coagulation. Along the same line, it has recently been suggested that anti-inflammatory therapy may be beneficial in DIC. Fibrinolysis in DIC patients is also inhibited, by release of PAI-1 and thrombin-activating fibrinolysis inhibitor

**FIGURE 1:** Key events in initiation phase of DIC. At the site of insult exposed TF complexes FVII, indirectly facilitating the production of a small amount of thrombin in the extrinsic tenase complex. This thrombin is enough to activate local platelets, which eventually provide the substrate for a “thrombin burst” through activation of the prothrombinase complex and the intrinsic tenase complex.
(TAFI) among other mechanisms[14].

Ultimately, the equilibrium reached between thrombin-mediated fibrin deposition and plasmin-mediated fibrinolysis becomes a determinant of the clinical presentation. Thrombin domination presents with microvascular occlusion and organ dysfunction; while plasmin dominance invokes diffuse bleeding[3].

Clinical Presentation

The presentation of DIC varies greatly. It is probably most often diagnosed in the setting of known abnormal coagulation studies in patients known to be at risk. While bleeding and organ failure are the most obvious signs for developing DIC [1], thrombin dominance versus plasmin dominance appears to determine whether organ perfusion failure or bleeding is more predominant in a given patient. In one series, 77% of patients with infections and DIC had organ failure, while in patients with obstetric disorders and DIC the prevalence of organ failure was less than 30% [1]. Physical exam findings consistent with organ perfusion failure include altered level of consciousness, purpura, oliguria, pulmonary edema, and gastrointestinal bleeding (from GI tract ischemia). Physical exam findings of the bleeding presentation are petechiae and purpura (petechiae portends dysfunctional or insufficient platelets, while purpura suggests depleted coagulant as well as anticoagulant factors[15]), epistaxis, hematuria, and oozing at puncture sites and surgical wounds.

The varying presentations of DIC have led to attempts to differentiate between a more fulminating course and a more protracted one. “Acute severe DIC” refers to the most fulminant presentation of the syndrome. These patients present initially with signs of multiple organ failure secondary to microcirculatory occlusion and rapidly progress to excessive bleeding as their factors, platelets, and anticoagulant proteins are consumed. The fulminant course of the syndrome is precipitated by widespread microcirculatory deposits of fibrin, which in turn initiates widespread micro- and macrocirculatory fibrinolysis. These two events precipitate simultaneous consumption of platelets and coagulant as well as anticoagulant factors. Although the first visible sign of DIC may be oozing from surgical or puncture sites, the initial microcirculatory trauma eventually makes itself known as organ dysfunction and eventually organ failure. The organ failure of microcirculatory occlusion can be insidious – CNS dysfunction may manifest simply as mental status change or confusion, renal failure a slow onset oliguria, pulmonary failure as progressive hypoxia. GI tract dysfunction is particularly troublesome as deterioration of perfusion to the GI tract makes bacterial translocation more likely[16] (may predispose patients to sepsis[17]) and promotes GI bleeding – which may be catastrophic in the absence of functional hemostatic mechanisms. Early diagnosis and treatment of DIC probably improves survival in DIC.

Low grade DIC, on the other hand may exist in a quiescent state with minimal symptoms for days or weeks[18]. In this case the mechanism is persistent expression of procoagulant material into the systemic circulation from a point (or points) source. The presentation of low grade DIC varies with the insult. Acute promyelocytic leukemia produces a low grade DIC characterized by bleeding, while other malignancies most frequently produce venous thromboses[3, 7]. The retained dead fetus syndrome has a variable presentation[3], while aortic aneurysms tend to produce[19] bleeding. It is important to recognize, however, that low grade DIC has the potential to become severe acute DIC, and that this may be a lethal progression. As patients with low grade DIC may be outpatients, a high index of suspicion is warranted if the patient is known to have a predisposing condition.

Diagnosis of DIC

There is no single definitive diagnostic test for DIC[20], although the search for laboratory markers has been the subject of vigorous efforts[21-24]. Numerous tests have been subjected to evaluation for sensitivity, specificity, and positive predictive value for DIC – always against a multimodal standard since there is no gold standard test for DIC. Reduced platelet count has a sensitivity of 73-96% but is non-specific. Elevated fibrin degradation products (FDP) has a sensitivity of 75-100% but is only 54% specific, and elevated D-dimer is 70-100% sensitive with a 46% specificity[25]. A recent study of patients clinically suspected of having DIC (what lead to clinical suspicion was not defined) found the two assays of elevated D-dimer titers and FDP to be 91% sensitive and 94% specific[23] when evaluated together; thus the need for formal laboratory evidence of procoagulant activation and inhibitor consumption is not entirely clear. Though the hypercoagulable state is relatively hard to diagnose early in the laboratory (except with TAT), thromboelastography (TEG) has been used to diagnose and follow the course of the hypercoagulable state after trauma.

Elevated APTT, INR and low fibrinogen and platelet count are not specific in the diagnosis but may be helpful in evaluating and treating the resulting coagulopathy.

More recently, specialty lab tests as thrombin-antithrombin (TAT) complexes are 98% sensitive, and soluble fibrin monomere (SFM) 81% sensitive and also more
specific for DIC. SFM is now offered in many hospitals as part of routine laboratory workup. Fibrinopeptide A is another breakdown product of fibrinogen by thrombin that is elevated in DIC. PAI-1 levels can be high in sepsis and DIC, indicating suppressed fibrinolysis, with risk for microthrombi and MOF. Although not available everywhere, AT and PC levels may be low as signs of elevated thrombin production and exhaustion of coagulation modulation.

Unlike other disorders (Alzheimer’s disease, for example) in which the diagnosis is difficult in the absence of a definitive test result, the diagnosis of DIC is usually attended by a wealth of evidence. Although a formal consensus definition of the disorder does not yet exist, the definition of Bick[26] sums the approach of most authors: DIC is diagnosed in the presence of a clinical syndrome known to cause DIC and with laboratory evidence of procoagulant activation, fibrinolysis, inhibitor consumption, and organ dysfunction.

The differential diagnosis of DIC includes many other disorders of coagulation. DIC is distinguished largely by the evidence of multimodal coagulopathy, particularly active fibrinolysis. Acute synthetic liver failure can present with bleeding and elevated INR first, followed by elevated PTT, and fibrinolysis is seen occasionally.

Vitamin K deficiency classically elevates the INR alone. Heparin induced thrombocytopenia (HIT/HITT) and the immune thrombocytopenias will decrease platelet count but rarely involve the synthetic arm of the coagulation system. Thus the presence of a clinical syndrome associated with DIC and laboratory evidence of fibrinolysis (positive d-dimers or FDP) should provoke great concern especially in the setting of any evidence of end-organ dysfunction.

Treatment

DIC is a complex disorder that universally occurs in the setting of other severe systemic illness. In acute severe DIC, it is mandatory to transfer the patient to the ICU where monitoring and frequent blood draws can enable the intensivist to closely follow the course and the effect of treatment. In chronic DIC this may be achieved at a less elevated level of care. However, the basic steps are the same for all types of DIC:

1) Treat the underlying disorder aggressively (when possible)
2) Restore adequate circulatory volume (if low)
3) Act to restore coagulation potential as quickly as possible (if bleeding)

Nonspecific Treatment

Attention must be paid to the core components of critical care. Airway management, appropriate restoration of blood volume (especially in bleeding trauma patients) and adequate delivery of oxygen should be closely monitored. In coagulopathic patients, correct the coagulopathy (as per below) before inserting central venous lines. Airway management may be complicated by tissue edema and blood in the airway thus personnel with appropriate airway skills should be available.

Hypovolemic patients with DIC may need fresh frozen plasma or other products to correct their coagulopathy and this need should be taken into account when planning volume resuscitation. If pressors or inotropes are necessary to ensure adequate organ blood flow, the choice of drug must be made with the knowledge that microcirculatory flow is already impaired by fibrin deposition so inotropes may be preferred over peripheral vasoconstrictors. Management of acute derangement of electrolytes and other metabolic deviations must take into account the potential for impending organ failure – particularly renal failure.

Treatment of Coagulopathy

Although there is no evidence either that prophylactic administration of blood products improves outcomes or that administration of blood products worsens outcome in DIC[27], it is vital to restore coagulation potential. As patients with acute DIC are at significant risks their coagulopathy should be corrected with necessary blood products. Restore oxygen delivery by assuring adequate Hb, SaO2 and Cardiac output. Mixed venous saturation (SvO2) can be monitored to assess the appropriateness of oxygen delivery. Platelets should be given to bleeding patients who have platelet counts under 50,000. Fresh frozen plasma should be given to bleeding patients with elevated INR >2.0 and/or PTT > 1.5 X normal, and in the event of significant hypofibrinogenemia (<100) give cryoprecipitate.

Specific Therapy for DIC

Heparin

The thinking behind the use of heparin in DIC is that preventing the activation of procoagulant mechanisms would reduce the tempo of the syndrome. There is some scant evidence that low dose heparin (5–10 U/kg/hr) is effective particularly in patients with thrombotic DIC of malignancy (Trousseau’s syndrome[28]), amniotic fluid embolism and for giant hemangiomas (Kasabach-Merritt
syndrome). However, large prospective trials of Heparin in DIC are lacking. Nonetheless, it appears reasonable to anticoagulate patients if there are signs of ischemia from gut or acral ischemia (ears, nose, fingers). Heparin does not appear to increase the risk of bleeding in DIC patients. In chronic DIC, long term therapy with LMWH appears to be a reasonable choice until the underlying factor is controlled. Warfarin is often ineffective for long term control.

There is more recent research on the heparinoid danaparoid in DIC. Like LMWH, it has 22X greater specificity for FXa than for thrombin. In the only trial published to date compared to heparin, 61.9% of danaparoid treated patients had symptomatic reduction of DIC while 62% of the heparin treated patients had no improvement or aggravation of symptoms, although there was no difference in outcome between groups[29]. The downside with all heparins (unfractionated, LMWH, heparinoid) is that they require AT to work, and AT deficiency is common in DIC. Therefore, heparin resistance is common in DIC. If so, AT levels need to be monitored and repleted if necessary. Direct thrombin inhibitors do not require AT for its action, but no trials on their use in DIC have been published.

The new pentasaccharides are selective for activity on FXa and are currently undergoing clinical trials. They have not been trialed for DIC as of date.

**Antifibrinolytic Drugs**

There is great concern in the use of antifibrinolytic agents (tranexamic acid, epsilon-aminocaproic acid, and aprotinin), in a state when secondary fibrinolysis is what keeps the microcirculation open. The literature soundly cautions the use of these agents[4]. This said, in promyelocytic leukemia, heparin and antifibrinolytics have been used to cover the remission induction period. Most hematologists would not use an antifibrinolytic until the patient is first heparinized.

**Coagulation modulator therapy**

Because tissue factor has such an important initiating role in DIC, TFPI has been studied in sepsis but preliminary data have not shown any patient benefit.

Active research into the coagulation modulation of sepsis has led to better understanding of the mechanisms involved and led to speculation that direct modulation of pro- and anti-coagulant mechanisms with endogenous modulators may be effective. It is known that antithrombin (AT) is a significant component of endogenous modulation of coagulation, that some patients with DIC (and sepsis too) have decreased AT levels, and that decreased levels of AT are correlated with worse outcomes[30]. Given this line of thinking, a number of trials have evaluated administration of AT to patients with sepsis related DIC, and therapy with AT is common in some settings[31]. Meta analysis of several of the trials has suggested that AT reduces mortality[27], but a large prospective trial failed to show benefit, possibly due to the confounding factor of heparin in this study. Further trials are required to better understand its potential role and define which patients that may benefit from AT supplementation.

Protein C is similarly important in preventing pathologic coagulation, is known to be deficient in many patients with DIC, and deficiency is associated with worse outcome[32]. A recent randomized prospective double-blind trial of APC versus heparin in patients with DIC found a significant reduction in bleeding and a significant reduction of 28d mortality from 40% to 20.4% (p < .05) in the APC treated group[33]. APC also has been shown to benefit patients with meningococcemia-induced DIC and in purpura fulminans associated with PC deficiency. APC is the first treatment shown in large prospective trials to be effective in DIC. APC is currently marketed as Xigris® and as such is widely available. It is likely that further treatment experience and studies in DIC patients will further define the role of this molecule.

Recombinant factor VIIa (rFVIIa) is another new drug which appears to have some promise for treating decompen-sated DIC. It is known that supraphysiologic doses of rFVIIa may compensate for deficiencies of factor VII, VIII, or IX and may also activate TAFI. Currently, only a few case reports are published on using rFVIIa in decompensated DIC[34, 35]. The concern with this medication is that it may induce thrombosis, even though the most recent safety data for this drug to date (Oct 2003) does not show increased risk for thrombosis. However, use of rFVIIa has been very limited.

Another molecule of future interest is the site inactivated recombinant factor VIIa (rFVIIai), currently used for preliminary animal studies in trauma (and in short supply). It will specifically block TF and thereby prevent coagulation activation, but is far from the clinical arena.

**Conclusions**

DIC is a common finding in intensive care unit patients. It is a symptom of an underlying disease, and because of the heterogeneity of the disorders that cause DIC, the presentation may vary significantly from patient to patient. The clinical syndromes of DIC range from low grade to
acute severe and the specific pathophysiology of the causative illness is what determines the presentation of DIC. Acute severe DIC is a medical emergency, which is frequently fatal and must be treated aggressively.

Diagnosis of DIC can be a challenge given the lack of a gold standard test and the number of disorders of coagulation in the differential diagnosis. However, a disciplined process which requires the presence of a known predisposing clinical syndrome, specific markers of fibrinolysis, and coagulopathy, can make the diagnosis with high sensitivity and specificity.

Treatment of DIC focuses on the treatment of the underlying disorder. Adequate monitoring in the ICU for acute DIC is mandatory. Coagulation potential should be restored as soon as possible with blood products in the face of clinical bleeding. While APC has been shown to be effective in DIC, ongoing trials will define the role of other coagulation modulators in DIC.

References


