



ICU Management: Disseminated Intravascular Coagulation (DIC)

33

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Learning Objectives

In this chapter, the readers will learn the following points concerning DIC in trauma:

- The definition, diagnosis, phenotypes, and time courses of DIC.
- The pathophysiology of cytokines, PARs, DAMPs, and NETs involved in DIC.
- The multiple effects of thrombin on platelets, coagulation, fibrinolysis, and inflammation.
- How DIC-induced MODS and critical bleeding affect a patient's outcome.
- How to manage DIC in order to improve a patient's outcome.

33.1 Introduction

Disseminated intravascular coagulation (DIC) is an acquired syndrome characterized by systemic activation of coagulation not restricted to the site of insults and can be caused by non-infectious and infectious insults [1]. The two major insults that evoke DIC are trauma and sepsis, which induce systemic inflammatory response syndrome (SIRS) [1, 2]. In the early 1990s, SIRS was considered the main cause of organ dysfunction affecting a patient's outcome [2]. Based on this concept, many randomized controlled trials targeting the control of SIRS were performed; however, none of these trials managed to achieve their aims, thereby suggesting that a change in the treatment strategies for controlling only SIRS [3]. Concurrently with this paradigm shift, tight molecular links between inflammation and coagulation were detected, in which thrombin plays a central role, resulting in multiple organ dysfunction syndrome (MODS) and eventually death [4]. DIC represents dysregulated inflammatory and coagulofibrinolytic responses to the insults such as trauma and sepsis; therefore, DIC can induce the development of MODS via the bidirectional interplay between inflammation and coagulation [1].

Penner summarized the trauma studies, including head trauma, published during the 1990s [5]. In those studies, DIC patients showed high inflammatory cytokines levels and increased systemic

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thrombin generation as measured by thrombin antithrombin complex (TAT) or prothrombin fragment 1 + 2 (PF1 + 2) immediately after trauma. These changes were associated with MODS and higher mortality rates than in non-DIC patients. In 2001, the International Society on Thrombosis and Haemostasis (ISTH) published a definition and diagnostic criteria for DIC [6]. This official communication positioned trauma (polytrauma, neurotrauma, fat embolism, etc.) as the main cause of DIC and stated that generalized inflammatory responses to insults with the release of cytokines from multiple inflammatory cells lead to extensive damage of the microvascular endothelium, which can result in organ dysfunction. Following this announcement, close relationships among trauma, inflammatory responses, microvascular disturbances, DIC, and MODS have been identified by the mid 2000s [7–9].

The ISTH again confirmed that tissue damage, including major trauma, is a cause of DIC with a high level of evidence about two decades after the first announcement [10]. DIC is an old disease with a history of over half a century; however, it is still a key disease to be recognized and diagnosed in the critical care setting [11]. In this chapter, the management of DIC in the intensive care unit (ICU) will be reviewed and discussed with the goal of improving the prognosis of critically ill trauma patients.

33.2 Trauma-Induced Coagulopathy and DIC

Trauma-induced coagulopathy is defined as the pre-stage of full-blown DIC, such as sepsis-induced coagulopathy. Three subcommittees of the ISTH published an official announcement, noting that dysregulated inflammatory and coagulofibrinolytic responses to trauma converge the trauma-induced coagulopathy in the final pathway of DIC [12] (Fig. 33.1). If trauma is sufficiently severe, however, DIC develops immediately after trauma without first proceeding through the stage of trauma-induced coagulopathy [13]. Expanding our understanding of these relationships between trauma-induced

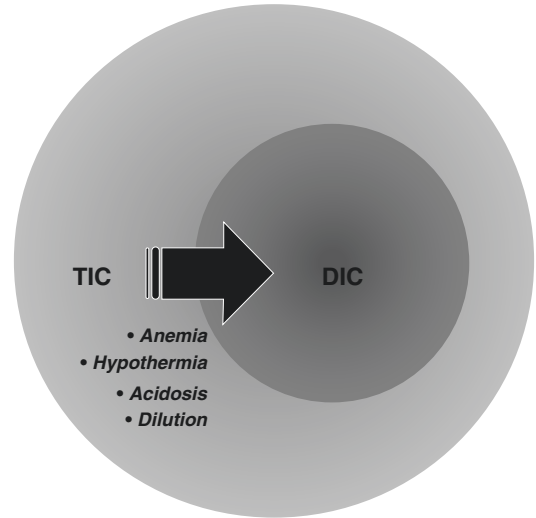


Fig. 33.1 Relationship between trauma-induced coagulopathy (TIC) and disseminated intravascular coagulation (DIC). TIC is defined as the pre-stage of full-blown DIC. If trauma is sufficiently severe, dysregulated inflammatory and coagulofibrinolytic responses to trauma converge in the final pathway of DIC. Exogenously induced secondary coagulopathies such as anemia-, hypothermia-, acidosis-, and dilution-induced coagulopathies, modify DIC

coagulopathy and DIC will likely provide therapeutic benefit to severely injured trauma patients.

Another point of note is that trauma-induced coagulopathy comprises primary and secondary coagulopathies [12, 14] (Table 33.1). Trauma-itself-induced primary coagulopathy, namely DIC, is modified by the anemia-, dilution-, hypothermia-, and acidosis-induced secondary coagulopathies.

33.3 The Definition and Diagnosis

33.3.1 The Definition

The ISTH defined DIC as “DIC is an acquired syndrome characterized by the 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” [6]. The key points of this definition are systemic thrombin generation not restricted to the insult’s site and endothelial cell activation followed by subsequent injury.

Table 33.1 Summary of trauma-induced coagulopathy

1. Physiological changes
(a) Hemostasis and wound healing
2. Pathological changes
(a) Trauma-itself induced primary coagulopathy
• DIC
– Activation of coagulation
– Insufficient anticoagulant mechanisms
– Increased fibrin(ogen)olysis (early phase)
– Suppression of fibrinolysis (late phase)
– Consumption coagulopathy
(b) Exogenously induced secondary coagulopathies that modify DIC
• Anemia-induced coagulopathy
• Hypothermia-induced coagulopathy
• Acidosis-induced coagulopathy
• Dilutional coagulopathy
• Others

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DIC disseminated intravascular coagulation

The ISTH further states that DIC is accompanied by the loss of tight junctions between endothelial cells which gives rise to capillary leak syndrome [6]. Excessive thrombin generation and endothelial injury with microvascular thrombus formation leads to decreased oxygen delivery to the cells and tissues and subsequent exhaustion of platelets and consumption of coagulation factors, causing MODS and oozing-type bleeding [6]. Therefore, DIC has long been recognized as “thrombohemorrhagic disorder” [15–17]. The definition of DIC established by the ISTH has provided a logical base concerning the pathophysiology of DIC.

33.3.2 The Diagnosis

The ISTH proposed overt DIC diagnostic criteria involving two steps; assessing underlying clinical conditions that may be associated with DIC and applying an algorithm for the diagnosis of DIC [6]. Before using the algorithm, a risk assessment to check whether or not a patient has an underlying disorder is mandatory. If a patient has such a disorder, algorithm may be applied. The ISTH overt DIC scoring system was prospectively validated in diverse patients including trauma admitted to the ICU [18]. The results confirmed a sufficient diagnostic accuracy of the ISTH scor-

ing system for diagnosing DIC in ICU patient clinically suspected of having this syndrome.

To diagnose DIC during its latent period before progression to full-blown overt DIC, the ISTH proposed non-overt DIC diagnostic criteria as well [6]. However, the prospective validation of non-overt DIC diagnostic criteria failed to prove the progression of non-overt DIC to overt DIC [19, 20]. To overcome this drawback associated with non-overt DIC diagnostic criteria and the low sensitivity for diagnosing DIC using the overt DIC diagnostic algorithm, the Japanese Association for Acute Medicine (JAAM) established the JAAM DIC diagnostic criteria. The JAAM diagnostic criteria have been prospectively validated in a critical care setting several times [20–22]. These studies showed that the JAAM DIC diagnostic criteria were able to identify DIC patients with high sensitivity and moderate specificity, and that the DIC diagnosed according to the JAAM criteria progresses to the ISTH overt DIC. Of note, the JAAM DIC diagnostic criteria can be applied at an early stage of trauma as well as a late stage with acceptable validity for the DIC diagnosis [23–25]. The ISTH and JAAM DIC diagnostic criteria can be found elsewhere [6, 21].

33.4 Phenotypes and Time Courses

33.4.1 Phenotypes

DIC comprises fibrinolytic and thrombotic phenotypes [1, 26–28]. DIC essentially is a thrombotic phenotype, and that DIC with a fibrinolytic phenotype is defined as the coexistence of DIC and pathological systemic fibrin(ogen)olysis [26, 28]. A condition wherein one insult simultaneously evokes DIC (with a thrombotic phenotype) and pathological systemic fibrin(ogen)olysis is called DIC with a fibrinolytic phenotype (Fig. 33.2).

Typical conditions that induce DIC with a fibrinolytic phenotype are acute promyelocytic leukemia [29], a long hypoxic state (e.g., asphyxia and drowning) [30], cardiac arrest and resuscitation [31], postpartum hemorrhagic shock [32],

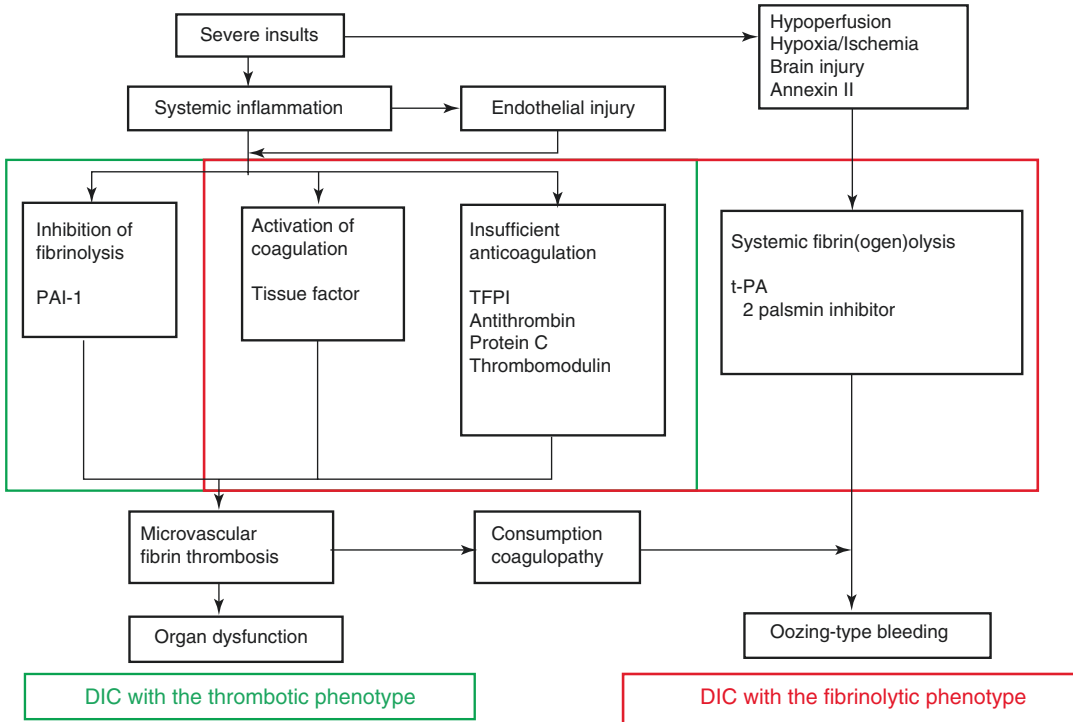


Fig. 33.2 Two phenotypes of disseminated intravascular coagulation (DIC). DIC essentially is a thrombotic phenotype; DIC with a fibrinolytic phenotype is defined as the coexistence of DIC and pathological systemic fibrin(ogen)olysis due to tissue hypoperfusion, systemic hypoxia/ischemia, etc. A condition wherein one insult simultaneously evokes DIC (with thrombotic phenotype) and pathological systemic fibrin(ogen)olysis is called DIC with a fibrinolytic phenotype.

Importantly, massive thrombin generation due to the activation of the tissue factor-dependent coagulation pathway and insufficient anticoagulation controls always underlie both types of DIC. *PAI-1* plasminogen activator inhibitor-1, *TFPI* tissue factor pathway inhibitor, *t-PA* tissue-type plasminogen activator. (Modified with permission (Creative Commons Attribution International License) [28])

isolated traumatic brain injury (iTBI) [33, 34], and severe trauma [35, 36]. The assembly of plasminogen and tissue-type plasminogen activator (t-PA) on promyelocytic leukemia cell surface-expressed annexin II promotes the conversion of plasminogen to plasmin [1, 29]. Common pathomechanisms increasing fibrin(ogen)olysis in asphyxia, drowning, cardiac arrest and resuscitation, postpartum hemorrhagic shock, and severe trauma are prolonged hypoxia- and ischemia-induced massive thrombin generation as well as marked t-PA release from endothelial Weibel-Palade bodies [1, 36–38]. Neurons and other cell types within the central nervous system synthesize and store t-PA in the granules and are rich in tissue factor, both of which are immediately released into the circulation in iTBI, causing DIC and systemic fibrin(ogen)olysis [39, 40]. All con-

ditions, except for acute promyelocytic leukemia, aggravate fibrin(ogen)olysis due to the time delay between the immediate release of t-PA and the delayed expression of plasminogen activator inhibitor-1 (PAI-1) mRNA [1, 7, 13, 35, 36].

33.4.2 Time Courses

The time courses in coagulofibrinolytic changes after trauma are shown in Fig. 33.3 [7, 35, 36]. The left side shows the physiologic state of hemostasis and wound healing, while the right side shows the pathological changes observed in DIC. These physiological and pathological states should be and can be distinguished using DIC diagnostic criteria. It is important to recognize, as the ISTH warned, that many published studies have discussed these

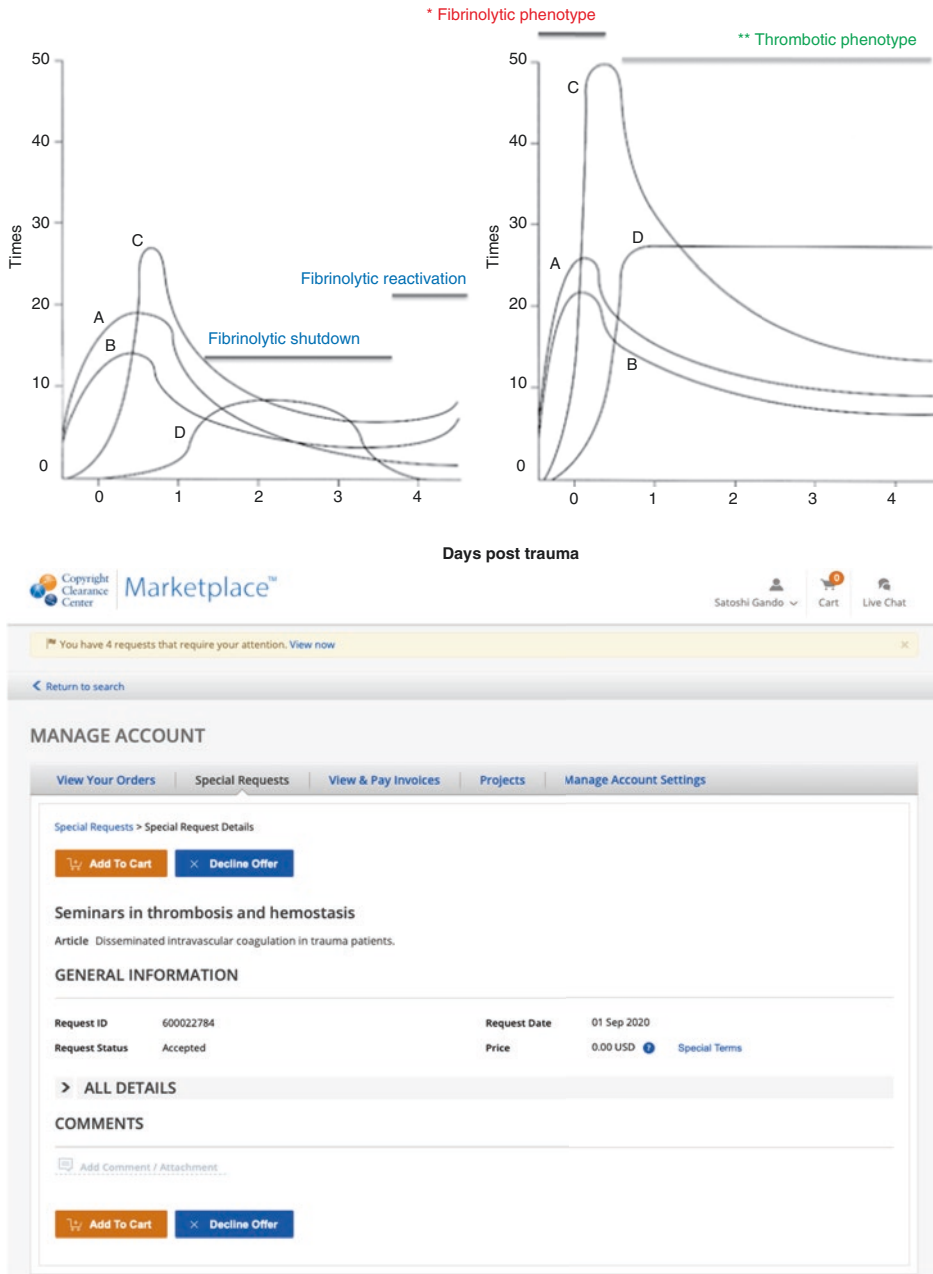


Fig. 33.3 Schematic diagrams of the variations in thrombin activity (A, measured by fibrinopeptide A, FPA), plasmin activity (B, fibrinopeptide B β 15–42, FPA β 15–42), fibrin formation and secondary fibrinolysis (C, D-dimer) from day 0 (in the emergency department) to day 4. Left, normal changes in hemostasis and wound healing. There are three phases of fibrinolysis: early activation, impairment (D, PAI-1: fibrinolytic shutdown), and reactivation. Normally, both the thrombin activity and PAI-1 are completely shut off by days 3–5 after trauma, followed by the reactivation of fibrinolysis. Right, pathological changes in DIC. There is a time

delay between immediate t-PA-induced massive plasmin generation and the induction of PAI-1mRNA, which causes systemic hyperfibrin(ogen)olysis (asterisk, DIC with a fibrinolytic phenotype), followed by the impairment of fibrinolysis due to persistent elevation of PAI-1 released from endothelial cells via transcription (double asterisk, DIC with a thrombotic phenotype). Persistent and systemic thrombin generation always underlies these changes in fibrinolysis. DIC disseminated intravascular coagulation, PAI-1 plasminogen activator inhibitor-1, t-PA tissue-type plasminogen activator. (Modified with permission [7])

two conditions without clear separation, confusing our understanding of trauma-induced coagulopathy and DIC [36, 41]. The main differences between these two time courses concerning the dynamics of thrombin generation and inhibition of fibrinolysis by PAI-1. Thrombin generation and inhibition of fibrinolysis transiently continues for several days under conditions of the normal hemostasis and wound healing but persist until DIC is improved under DIC conditions.

Figure 33.3 (right) further depicts the two phenotypes of DIC. The time delay between the immediate increases in plasmin generation due to t-PA release and delayed elevation of PAI-1 (single asterisk) indicates DIC with a fibrinolytic phenotype, and persistent increases in both thrombin generation and PAI-1 (double asterisk) indicate DIC with a thrombotic phenotype. Furthermore, DIC with a fibrinolytic phenotype exists only for a couple of hours after presentation to the emergency department [13, 31]; however, in cases of severe trauma, the fibrinolytic phenotype progresses to the thrombotic phenotype without complication of sepsis [42].

33.5 Pathophysiology

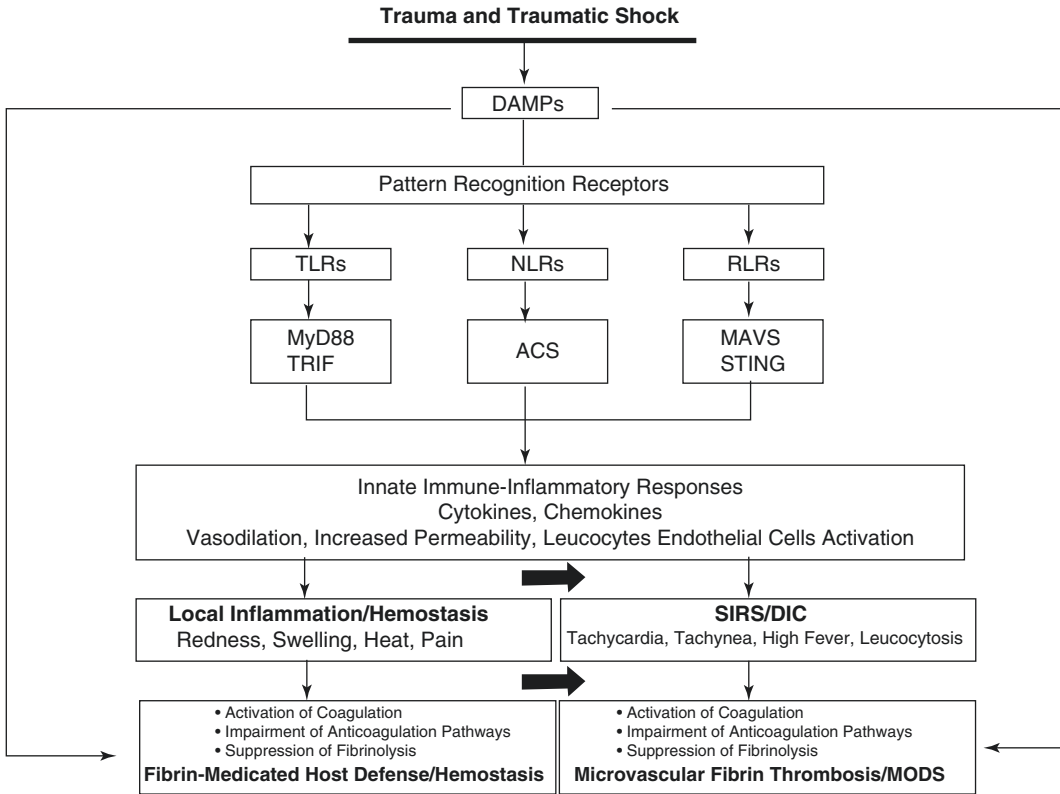
Although DIC develops in diverse underlying conditions, once initiated, the pathomechanisms that give rise to DIC are similar, regardless of the setting [1]. The modern pathophysiology of DIC and its characteristics in trauma were established around the 1990s [1, 5, 6, 35]. Recent advances

have been described in studies which highlighted bidirectional interplay among innate immunity, inflammation, and coagulofibrinolytic responses, in which histones and neutrophil extracellular traps (NETs) play central roles, constituting the main pathophysiology of DIC [43, 44].

Trauma induces innate immune responses via the altered-self, danger-associated molecular patterns (DAMPs), which are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-I-like receptors (RLRs). Signal transductions of PRRs leads to the expressions of pro-inflammatory cytokines (TNF- α , IL-1, IL-6) and chemokines (IL-8) as well as anti-inflammatory cytokines (IL-10) [28, 45, 46]. Innate immune responses activate inflammation, coagulation, endothelium, and complement pathways to maintain body homeostasis with the balance of inflammation and anti-inflammation called SIRS and compensatory anti-inflammatory syndrome (CARS), respectively [2, 47]. At the site of insults such as trauma and sepsis, hemostatic thrombosis and immunothrombosis formed by the activation of coagulation cascades and activated neutrophil-released NETs control the insults (hemorrhage and infection), delimits and fixes the insult-induced injuries, and protects the dissemination of DAMPs, pathogen-associated molecular patterns (PAMPs), and microorganisms into the circulation [28, 45, 46, 48]. However, if the insult is sufficiently severe, local physiological thrombosis spreads throughout the whole body and then pathological DIC associated with SIRS ensues [28, 48] (Fig. 33.4).

Fig. 33.4 Trauma elicits nonspecific innate immune inflammatory responses that limit and repair tissue damage. The figure depicts a simplified schematic representation of the activation of pattern recognition receptors by DAMPs and their signaling through the adaptor proteins. This cascade promotes the transcription of several pro-inflammatory cytokines and chemokines, leading to local and systemic inflammatory responses. Local inflammation begins as an adaptive host response, serving to promote the host defense and physiologic hemostasis and fibrin-mediated host defense called immunothrombosis. Spillover of the DAMPs and inflammatory cytokines into the circulation induces SIRS, which activates systemic coagulation, suppresses fibrinolysis, and overwhelms the anticoagulant control mechanisms that restrict hemostasis

locally, giving rise to DIC. Importantly, DAMPs themselves can activate coagulation and impair anticoagulation pathways through endothelial damage. ACS apoptosis-associated speck-like protein containing caspase recruit domain, *DAMPs* damage-associated molecular patterns, *DIC* disseminated intravascular coagulation, *MAVS* mitochondrial antiviral signaling, *MODS* multiple organ dysfunction syndrome, *MyD88* myeloid differentiation factor 88, *NLRs* nucleotide-binding oligomerization domain-containing receptors, *RLRs* retinoic acid inducible gene-I-like receptors, *SIRS* systemic inflammatory response syndrome, *STING* stimulator of interferon gene, *TRIF* toll/IL-1 receptor homology domain-containing adaptor inducing interferon β , *TLRs* toll-like receptors. (Modified with permission [45])



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33.5.1 Cytokines

Important pro-inflammatory cytokines that induce SIRS following trauma are TNF- α , IL-1, and IL-6. Immediately after trauma, significant increases in these cytokines have been confirmed in DIC and severely injured patients [49, 50]. TNF- α and IL-1 induce tissue factor expression on monocytes and endothelial cells and down-regulate endothelial protein C receptor (EPCR) leading to the suppression of the protein C anticoagulant pathway [51, 52]. IL-6 is also able to induce the activation of coagulation [53]. These inflammatory cytokines further activate neutrophils and endothelial cells [51], which upregulate or express adhesion molecules such as selectins, integrins, and immunoglobulin superfamily which elicit platelets, neutrophils, and endothelial cells interactions, leading to the release of neutrophil-mediated reactive oxygen species and neutrophil elastase [54–56]. Activated platelets and endothelial cells-upregulated P-selectin induces the expression of tissue factor on monocytes [1, 57]. Neutrophil-released reactive oxygen species and elastase injure endothelial cells, bringing about the dysfunction of anticoagulation systems comprising tissue factor pathway inhibitor (TFPI), antithrombin/glycosaminoglycan, and protein C/thrombomodulin on the endothelial cells and the glycocalyx [58, 59]. Furthermore, TNF- α induces immediate t-PA release followed by persistent expression of PAI-1, which impairs fibrinolysis [60–62].

Taken together, these findings indicate that inflammatory cytokines are capable of causing all pathomechanisms of DIC. The following pathomechanisms have been confirmed in DIC after trauma: SIRS [49, 63, 64], activation of platelets and systemic thrombin generation [64, 65], insufficient anticoagulant systems such as TFPI [66], antithrombin [36, 63, 65], protein C [36], activation followed by the impairment of fibrinolysis [31, 49, 67, 68] and endothelial cells activation and injury [35, 69, 70].

33.5.2 Protease-Activated Receptors (PARs)

Signals of coagulation proteases are transmitted to inflammatory cells via protease-activated receptors (PARs) [71, 72]. The PARs are G-protein coupled receptors with seven transmembrane domains that can sense signals from coagulation proteases with auto-activation mechanisms by the proteases-cleaved and exposed active sequence functioning as tethered ligand. The four known PARs are PAR1, PAR2, PAR3, and PAR4. Tissue factor/FVIIa complex activates PAR2, tissue factor/FVIIa/FXa ternary complex activates PAR1 and PAR2, and FIIa (thrombin) activates PAR1, PAR3, and PAR4, resulting in the inductions of varied effects on platelets, leucocytes, and endothelial cells [73, 74] (Table 33.2). Therefore, the PARs play pivotal roles in bidirectional interplays between inflammation and coagulation [43], which forms vicious cycles in DIC, leading to the development of MODS [1, 74].

33.5.3 DAMPs and NETs

Two epoch-making studies were published in the 2000s [75, 76]. One showed that NETs kill bacteria and another reported that extracellular histones are major mediators of death through endothelial injury and microvascular thrombosis in sepsis. Following these studies, DAMPs including histones and NETs containing neutrophil DAMPs such as DNA and histones became major mediators of many pathologic disorders including DIC [1, 48, 77, 78].

33.5.3.1 Cytokines and SIRS

Circulating mitochondrial DAMPs, mitochondrial DNA and formyl peptides, showed immediate and thousands-fold higher increases in severely injured trauma patients than control subjects, which were followed by the TNF- α and

Table 33.2 Protease-activated receptors (PARs) and their actions on platelets, leukocytes, and endothelium

	Induction of expression, release, etc.	Actions
Platelets	5-HT, ADP, TXA2, P-selectin, GP α Ib/ β 3	Platelet activation, adhesion, aggregation
Leukocytes	TNF- α , IL-6, IL-8, CD11b	Proinflammatory
	Tissue factor	Activation of coagulation
	Oxygen radicals	Endothelial cells injury
Endothelial cells		
	VWF, PAF	Platelet activation and consumption
	IL-1, IL-6, IL-1	Proinflammatory
	P-selectin, E-selectin, ICAM-1, VCAM-1, MCP-1	Endothelial cells activation
	MMP7, MMP9, Apoptosis	Apoptosis
	Tissue factor, PAI-1, TM down regulation	Activation of coagulation, suppression of fibrinolysis, and impairment of anticoagulation
	Nitric oxide, EDHF, histamine, gap formation	Vessels dilatation, increased permeability
	Endothelin	Vessels constriction

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5-HT 5-hydroxytryptamine, ADP adenine di-phosphate, TXA2 thromboxane A2, GP glycoprotein, TNF tumor necrosis factor, IL interleukin, VWF von Willebrand factor, PAF platelet-activating factor, ICAM-1 intracellular adhesion molecule-1, VCAM-1 vascular cell adhesion molecule-1, MCP-1 monocytes chemotactic protein-1, MMP metalloprotease, PAI-1 plasminogen activator inhibitor-1, TM thrombomodulin, EDHF endothelial hyperpolarizing factor

IL-6 expression associated with SIRS and organ dysfunction [79, 80]. Circulating histones rising to toxic levels immediately after trauma led to IL-6 release, systemic thrombin generation, endothelial injury, and NETs formation, which induced microvascular thrombosis and organ dysfunction [50]. These studies demonstrate

close relationships among innate immunity, SIRS, DIC, and MODS in trauma.

The bidirectional interplays between cell injury-induced histones triggering NETs formation and NETs as a source for localized and systemic histones are important in the pathomechanisms of DIC [48, 78]. The above-mentioned DAMPs-induced expression of cytokines and chemokines via PRRs is well recognized [28, 45, 48]. Histones and NETs also induce expression of TNF- α , IL-1, and L-6 via the signal transductions of PRRs, leading to development of SIRS [50, 81–83]. Rapid increases in these cytokines may be due in part to their release from presynthesized storage in addition to the induction of their expressions [50, 81].

33.5.3.2 Platelets and Coagulation

Histones directly or via interactions with TLR2 and TLR4 induce platelet activation and subsequent aggregation associated with P-selectin release and phosphatidylserine exposure, leading to thrombocytopenia in vivo and in critical illness [84–88]. Activated platelets and NETs collaborate to promote thrombin generation and intravascular coagulation [89].

Tissue factor expression on monocytes and its exposure on the endothelium due to endothelial injury is the most important trigger of DIC [1, 90]. Indeed, DIC patients after trauma shows high tissue factor levels associated with persistent thrombin generation [64, 91]. Extracellular histones induce tissue factor antigen, activity, and mRNA in endothelial cells via TLR2 and TLR4 [92, 93]. Histones are able to promote prothrombin auto-activation, which is an important finding indicating that thrombin is independently generated without the activation of coagulation cascades [94]. Furthermore, histone-induced phosphatidylserine exposures on red blood cells (RBCs) and endothelial cells enhance coagulation activation [93, 95]. Other DAMPs, including DNA contained in NETs and RNA released from injured cells, promote thrombosis dependent on the FXII/FXI-induced activation of contact pathways of coagulation [96–98], which is related to a poor prognosis of DIC [99].

33.5.3.3 Anticoagulant Systems and Endothelial Cells

The impairment of thrombomodulin-dependent protein C activation by histones increases thrombin generation, which is a main pathomechanism of DIC [100]. DIC induces capillary leak syndrome [1, 6]. Histone-induced endothelial injury contributes to increases in endothelial permeability [50, 75] and mitochondrial DAMPs also increase endothelial permeability [101], which gives rise to loss of antithrombin into the extravascular spaces [102]. Neutrophil elastase, a constituent of NETs, cleaves or degrades TFPI, protein C, and antithrombin [1]. High levels of neutrophil elastase associated with endothelial injury in DIC after trauma have been repeatedly confirmed [67, 69, 70]. Furthermore, *in vitro*, *in vivo*, and clinical studies of trauma and sepsis confirmed histone-induced endothelial injury by elevated levels of soluble thrombomodulin and its association with thrombin generation and microvascular thrombosis [50, 84]. These findings indicate that histones and NETs are deeply involved in the three major pathomechanisms of DIC; thrombin generation due to insufficient anticoagulant systems, endothelial injury, and capillary leak syndrome.

33.5.3.4 Activation and Impairment of Fibrinolysis

Extracellular DNA acts as a template for the activation of fibrinolysis under the conditions of neutralization by endogenous serpins such as PAI-1; however, under conditions of the over expressions of PAI-1, extracellular DNA has antifibrinolytic effects, which suggests the role of DNA in DIC [103]. Cell-free DNA binds to both plasmin and fibrin, forming ternary complex and consequently inhibiting fibrinolysis [104]. DNA, histones, and NETs were shown to delay t-PA-mediated fibrin clot lysis, and the former two further increased the fibrin clot fiber diameter, resulting in the thrombus stability [105, 106]. Although these results seem to be physiological effects of histones and DNA supporting the strength of immunothrombosis at the insult site, under the pathologic condition of DIC with increased levels of PAI-1, these DAMPs may

play pathological roles through the inhibition of fibrinolysis.

33.5.3.5 Brief Summary

In vivo experiments clearly showed that histones were able to decrease platelet counts and fibrinogen levels, and prolong the prothrombin time and activated partial thromboplastin time (APTT), which resulted in platelet and fibrin thrombosis associated with organ dysfunction and low survival probability [84]. Similar results were obtained in an experimental trauma model and in trauma patients [50]. As such, DAMPs, especially histones and NETs constitute the main pathophysiology of DIC [78].

33.5.4 Multiple Actions of Thrombin

The most important key factor in DIC is thrombin, which controls and influences all other factors associated with DIC [1] (Fig. 33.5). In addition to the fundamental role of thrombin in the formation of fibrin clots, thrombin enhances inflammation and activates platelets through PARs [71, 74]. On the surface of activated platelets, FIXa/FVIIIa (tenase) and FXa/FVa (prothrombinase) complexes induce thrombin burst, which accelerate thrombin generation about hundreds of thousands-folds [107]. The conversion of prothrombotic and inflammatory properties of thrombin into anti-thrombotic and anti-inflammatory actions can be done via complex formation with endothelial thrombomodulin [1, 43]. The thrombin thrombomodulin complex-formed activated protein C suppresses thrombin generation by the proteolytic degradation of FVa and FVIIIa. This complex also enhances the activation of TAFI by thrombin about 1250-fold [108]. The anti-inflammatory properties of thrombin complexed with thrombomodulin are exerted through several pathways, such as the binding of activated protein C and EPCR-induced changes in PAR1 inflammatory properties [1, 43, 109] and cleaving of carboxy-terminal arginine residues of bradykinin, C3a and C5a as well as osteopontin by TAFIa [110–112]. Thrombin-mediated fibrinolysis control also should be acknowledged. Thrombin stimulates fibrinolysis via immediate t-PA release

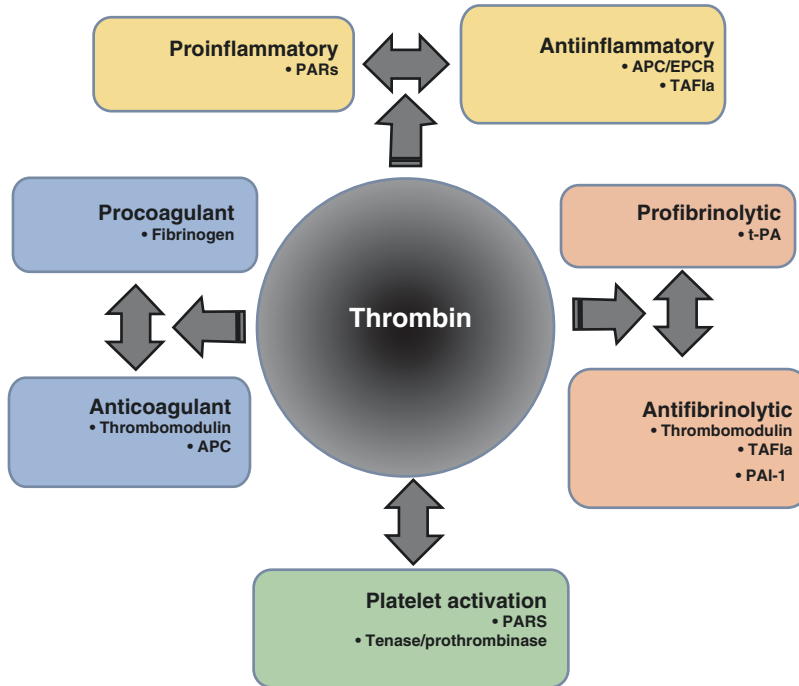


Fig. 33.5 Multiple actions of thrombin. Multiple actions of thrombin protect the fine balances in the physiological status to maintain homeostasis. Excessive thrombin generation in DIC upsets this balance and induces multifaceted consequences, leading to inflammation, thrombosis, and bleeding. For this reason, DIC has been described as thrombohemorrhagic disorder. Refer to the text for details.

APC activated protein C, *DIC* disseminated intravascular coagulation, *EPCR* endothelial protein C receptor, *PAI-1* plasminogen activator inhibitor-1, *PARs* protease-activated receptors, *TAFIa* activated thrombin activatable fibrinolysis inhibitor, *t-PA* tissue-type plasminogen activator

from endothelial Weibel-Palade bodies [37, 113]. In addition to the induction of PAI-1 expression in endothelial cells [114], thrombin inhibits fibrinolysis through TAFIa [108, 115, 116]. The thrombin thrombomodulin complex activate TAFI [108], and then TAFIa removes the carboxyl-terminal lysine from fibrin, leading to downregulation of fibrinolysis [115, 116].

Massive thrombin generation from immediately to several days after trauma has been repeatedly confirmed in DIC patients since the early 1990s [7, 9, 64, 65] and recent publications have successfully reproduced these results [13, 117]. Dumber and Chandler elegantly showed that immediate and excessive thrombin generation not restricted to injury sites is due to tissue factor activity in systemic circulation and that reduced antithrombin levels allow systemic thrombin generation to continue once started [118, 119].

Tissue factors in systemic circulation likely cause significant thrombin generation in DIC patients [120]. Substantial evidence of massive thrombin generation in DIC after trauma suggest that the manifestation of bleeding and thrombosis in DIC may be dependent on the fine balance of multiple actions of thrombin [1].

33.6 MODS and the Prognosis

Esmon et al. [4] announced that the molecular links between inflammation and coagulation are unquestioned and stated that the inflammation-coagulation autoamplification loop progresses to vascular injury and MODS, leading to death. The ISTH fully accept this concept and published statement that inflammation-induced systemic thrombin generation and endothelial injury give rise to MODS

[6]. DIC is a frequent complication of SIRS [63] and its prevalence increases in parallel with the severity of inflammation associated with stepwise increases in organ dysfunction [121].

DIC patients after trauma consistently showed significantly higher prevalence of MODS and rates of mortality than in non-DIC patients [49, 65, 66, 68–70, 117]. DIC and sustained SIRS for more than 3 days after trauma have shown significant increases in tissue factor levels and thrombin generation for 5 days after trauma associated with high rates of MODS and death [64]. A clinical decision analysis confirmed these results while showing that likelihood ratios of SIRS for more than 3 days and DIC on day 1 for predicting MODS after trauma were 6.25 and 11.6, respectively, and that DIC and sustained SIRS were also significantly associated with high mortality [122]. Stepwise logistic regression analyses and multiple regression analyses with the stepwise method showed that the DIC scores immediately after trauma were independent predictor of massive transfusion and death of trauma patients [24, 25]. A multicenter prospective study confirmed that the area under the receiver operating characteristic curve showed significant performance of DIC score immediately after trauma for predicting MODS, massive transfusion, and patient death [123]. Therefore, irrespective of phenotypes, DIC is a leading cause of MODS and death, and the DIC score has a good performance for predicting poor prognosis in trauma patients. Furthermore, DIC has been recognized as an independent predictor of MODS and death regardless of underlying disorders [1].

33.6.1 Microvascular Thrombosis

Microthrombosis after trauma, including iTBI, has been well established [28, 124]. In 1969, McKay reviewed DIC in trauma and reported that a tissue examination of the disease revealed either or both platelet or fibrin thrombi in the arterioles, venules, and capillaries of a variety of organs such as the brain, pituitary gland, lungs, liver, kidneys, adrenal glands, and gastrointestinal tracts [16]. Sevitt et al. [125] showed thrombi

formation in the lungs of one patient who died within a few hours after trauma, a stage they called acceleration of fibrinolysis, which equals a period of DIC with a fibrinolytic phenotype [13]. They further confirmed frequent capillary microthrombosis within 3 h (24.4%) and during the next 9 h (37.9%) after injury in trauma patients. Within 48 h of injury, a total of 66.7% autopsied patients revealed thrombi formation [126]. In addition, many studies have produced the evidence supporting microvascular thrombosis in severe trauma [127, 128], in iTBI [129] and in DIC associated with such trauma [40, 130]. A study of iTBI comprising 88% of patients diagnosed as DIC demonstrated that large microthrombi were more commonly observed in autopsy in patients who died immediately after iTBI and that in addition to the brain/spinal cord, remote organ microthrombi formation such as in the liver, lungs, kidneys, pancreas, pituitary gland, thymus, and intestine was frequently observed [130]. The results clearly support the notion that coagulofibrinolytic changes in iTBI are not markedly different from those in trauma patients without head injury [131].

Microvascular thrombosis reduces oxygen delivery to cells and tissues, leading to MODS. Many clinical, experimental, and autopsy studies showing close correlations between microvascular thrombosis and tissue injury in many vital organs, including the brain, lungs, liver, and kidneys, support this theory [74]. However, microvascular thrombosis alone does not explain the pathomechanisms of MODS in DIC [132]; the bidirectional interplay between coagulation and inflammation should also be acknowledged. Pro-inflammatory cytokine-induced neutrophils and endothelial interactions and PAR-mediated amplification of coagulation and inflammation are important for MODS in DIC. TNF- α - and IL-1-induced thrombin formation upregulates P-selectin and induces the expression of E-selectin on the endothelium and L-selectin on the neutrophils, initiating neutrophils and endothelial interactions, and further promoting the expressions of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on the endothelial cells

[54–56, 133]. As a result, activated neutrophils adhering to endothelial cells secrete elastase, myeloperoxidase, and reactive oxygen species, leading to endothelial injury, which promotes thrombin generation and fibrin thrombosis, thus causing MODS [54, 58, 74, 134]. The activation of neutrophils and endothelial injury associated with MODS and the higher mortality rate in post-trauma DIC than in non-DIC patients has been confirmed [69, 70]. Although trauma-related studies are lacking, PARs, especially PAR1, PAR2, and PAR4, contribute to the development of MODS in sepsis through a vicious cycle of inflammation and fibrin thrombosis [73, 74]. Taken together, these findings suggest that microvascular thrombosis associated with endothelial injury is a primary cause of MODS in DIC.

33.6.2 Histones and NETs

In addition to microvascular thrombosis associated with neutrophil activation-induced endothelial injury, DAMPs, especially histones, and NETs are now considered a major pathogenesis of MODS both in trauma and sepsis, especially in patients complicated with DIC [76–79, 84, 135]. In clinical settings, histones and NETs are involved in the development of DIC [136–138], MODS [139–141], and high mortality [138, 142] both in trauma and sepsis. Furthermore, experi-

mental studies have shown that histones can cause brain, cardiac, lung, liver, and renal injuries [50, 78, 84].

The pathomechanisms of MODS in DIC caused by histones and NETs can be attributed to their pro-inflammatory, procoagulant, antifibrinolytic effects as well as endothelial injury associated with insufficient anticoagulant systems [78]. In addition to these indirect mechanisms, histone-mediated direct cellular injuries are deeply involved in the development of MODS. Sera from patients with high levels of histones showed a reduced viability of cells derived from the heart, lung, liver, and kidney as well as cultured endothelial cells [141]. A previous study showed the histone-induced promotion of Ca^{2+} influx without intracellular Ca^{2+} mobilization [143]. However, histones bind to endothelial cells and cardiomyocytes, and then induce Ca^{2+} influx and overload with consequent pore formation, leading to endothelial injury and cardiac dysfunction [50, 140]. In cecal ligation and puncture models of sepsis, the accumulations of histones and neutrophils was observed in lungs, liver, kidneys, and spleen suggesting NETs formation [144]. Taken together, these findings indicate that histones and NETs as a source of histones synergistically cause MODS and DIC both in indirect and direct ways and affect the outcomes of the trauma and sepsis patients. These pathomechanisms in DIC are shown in Fig. 33.6 [78].

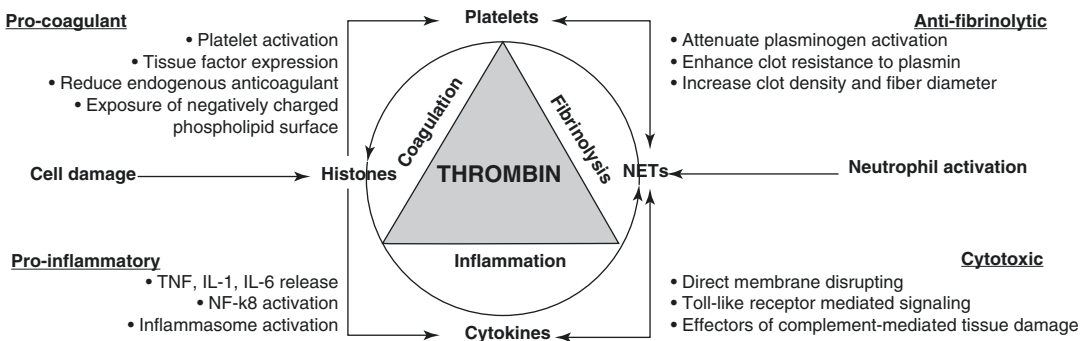


Fig. 33.6 Bidirectional interplays between histones and NETs in DIC. Histones and NETs as a source of histones synergistically induce inflammation, platelet and coagulation activation, insufficient anticoagulation control, inhibition of fibrinolysis, and cytotoxic effects on cells. Thrombin genera-

tion as a result of these processes plays a central role in the cross talk between inflammation and coagulofibrinolytic changes. *DIC* disseminated intravascular coagulation, *NETs* neutrophil extracellular traps. (Modified with permission (Creative Commons Attribution International License) [78])

33.7 Management

In the ICU, trauma patients suffer from DIC due to two conditions; trauma itself-induced DIC and complicated sepsis-induced DIC. Because DIC with a fibrinolytic phenotype continues only for a few hours after injury and then progresses to a thrombotic phenotype [13, 42], a majority of DIC diagnosed in the ICU are considered to be the thrombotic phenotype. Whether the etiology involves trauma or sepsis, the same managements approach is applied to thrombotic phenotype DIC [1]. The following descriptions are based on the findings of studies on sepsis; however, findings can also be applied to the management of DIC in severely injured trauma patients in the ICU.

33.7.1 Rationale

33.7.1.1 Why

Innate immune, inflammatory, and coagulofibrinolytic responses maintain the body's homeostasis against the insults, such as trauma and sepsis. However, if an insult is sufficiently severe, these physiological responses transform into pathological dysregulated inflammatory and coagulofibrinolytic responses (namely DIC), which affects the patient's outcome due to the disturbance of homeostasis by the development of MODS (Fig. 33.7). The failures of all randomized controlled trials targeting SIRS [3] led to the understanding that bidirectional interplay between innate immunity, inflammation, and coagulation is key to the improvement of the outcome of critical illnesses [4, 43, 44]. In addition, the need to target not only pathological responses but also all components (including the insult itself and MODS) affecting the outcome as a whole is now recognized worldwide. For these reasons, DIC as pathological responses, as well as the insult itself, such as trauma, and MODS need to be treated simultaneously in order to improve a patient's outcome [1].

33.7.1.2 To Whom

Megatrials of anticoagulants, activated protein C and antithrombin, for all populations of sepsis

have failed [145, 146]. Following these failures, substantial evidences has been accumulated regarding the actual target patient population. Subgroup analyses of these megatrials have shown that anticoagulants are effective only against sepsis-induced DIC [147–149]. Following these publications, knowledge concerning immunothrombosis progressing to DIC has spread worldwide, promoting the understanding that ambiguous treatment with anticoagulants at the stage of immunothrombosis may deteriorate the body's physiologic responses [48]. Furthermore, a meta-analysis and systematic reviews of randomized controlled trials for anticoagulant therapy in sepsis clearly have shown that the specific target populations are neither whole sepsis patients nor patients diagnosed as “coagulopathy” but patients with a definite diagnosis of DIC [150, 151]. Therefore, the treatment target of anticoagulants therapy is definitively diagnosed DIC [1].

Post hoc analyses of the megatrials showed that anticoagulants have high degree of effectiveness in patients with high risk of death as evaluated by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score II (SAPS II) [152, 153]. In systematic reviews and meta-analyses for anticoagulants, meta-regression analyses confirmed significant negative correlations between the effect size of anticoagulant therapies and baseline mortality rates in individual studies, suggesting that the beneficial effects of anticoagulants increase with increasing baseline risk [154, 155]. A multicenter cohort study further proved that anticoagulant therapy was associated with a better outcome according to the deterioration of both DIC scores and APACHE II scores [156] (Fig. 33.8). The second key point concerning the target population in addition to a diagnosis of DIC, therefore, is disease severity, and a SOFA score of 13–17 or APACHE II score of 24–29 may be the therapeutic ranges [157].

The third key point concerns heparin administration. Concomitant heparin use with anticoagulants consistently induced the deterioration of the drug effects and was associated with bleeding

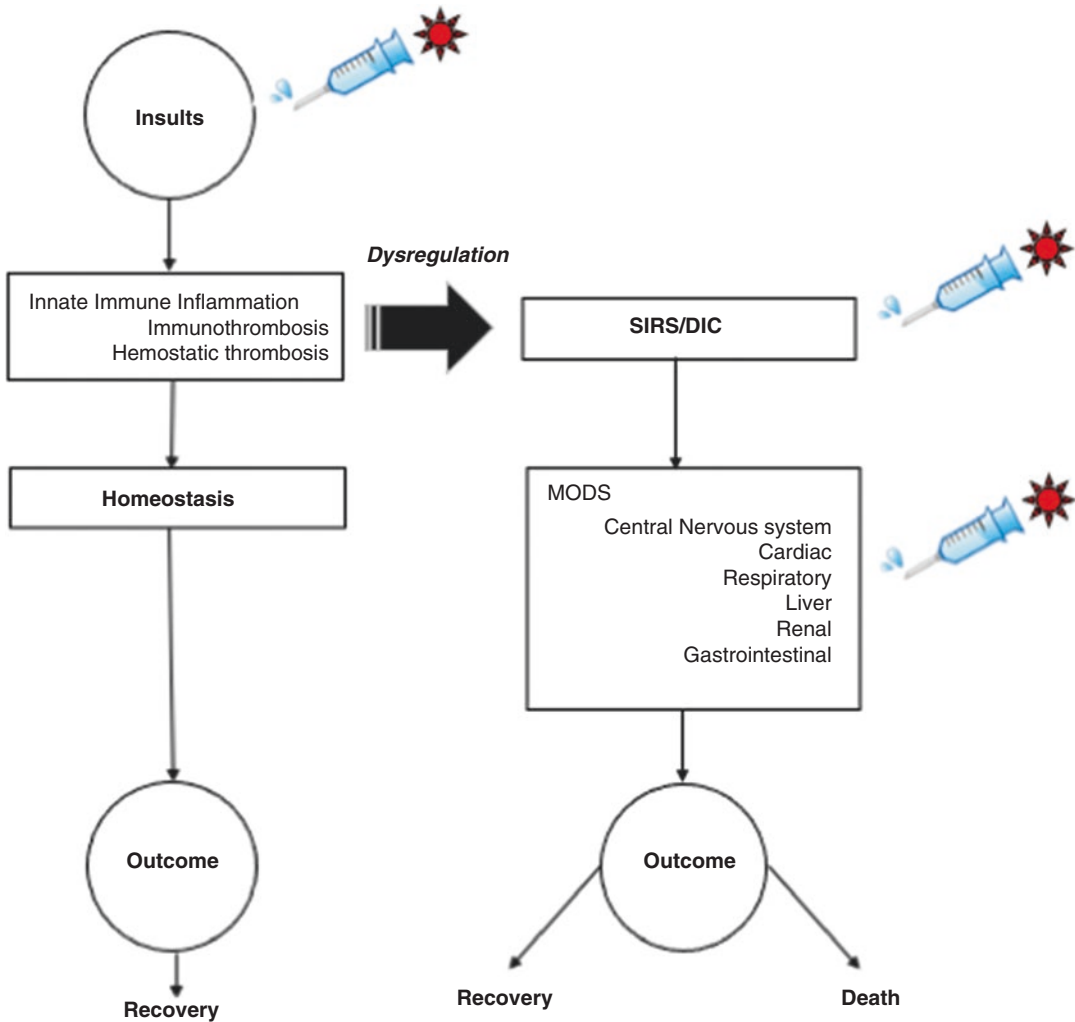


Fig. 33.7 Innate immune inflammation, and coagulation and fibrinolysis maintain body homeostasis via immunothrombosis and hemostatic thrombosis against the insults. However, if the insult is sufficiently severe, physiological body responses become dysregulated and pathological SIRS and DIC develop, giving rise to MODS, which affects the patient’s outcome. To improve the out-

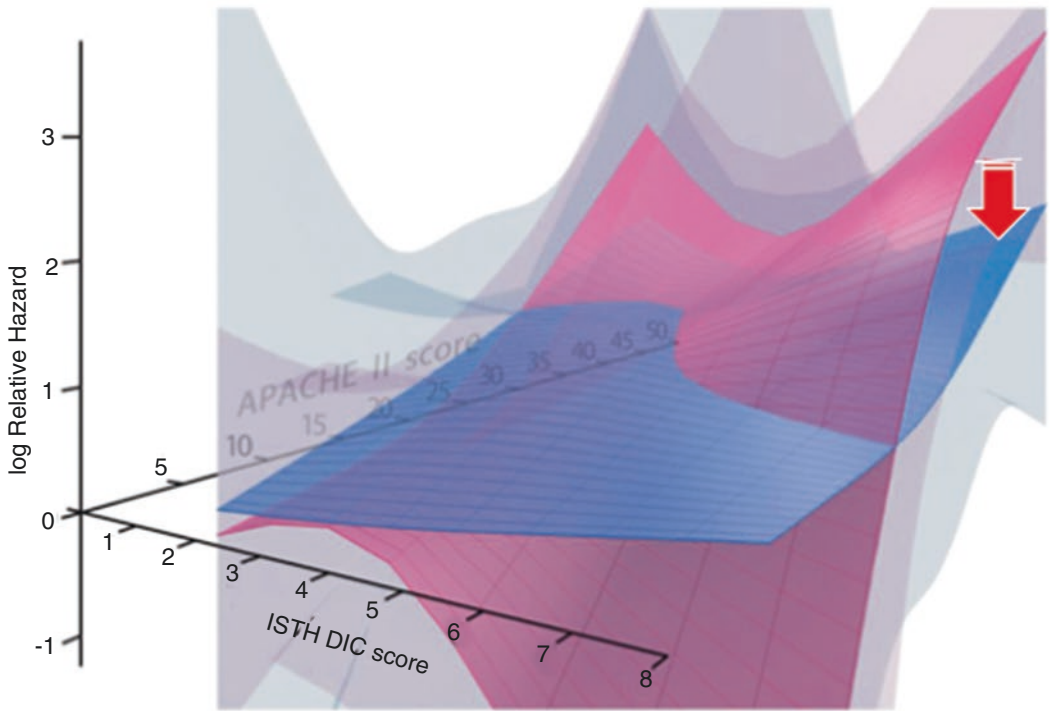
come, both the insult and dysregulated inflammatory and coagulofibrinolytic responses, namely SIRS and DIC need to be treated simultaneously. In addition, artificial organ supports, such as a ventilator, renal replacement therapy, etc., are also needed. *DIC* disseminated intravascular coagulation, *MODS* multiple organ dysfunction syndrome, *SIRS* systemic inflammatory response syndrome

complications [158, 159]. The concomitant use of anticoagulants for DIC and a prophylactic dose of heparin for venous thromboembolism should therefore probably be avoided.

Taken together, these findings indicate that the treatment targets are critically ill patients with DIC and a high trauma severity without concomitant heparin use.

33.7.1.3 When

Both the ISTH and JAAM recommend conducting repeated evaluation of DIC scores for the diagnosis and subsequent treatments [6, 22]. Nobody object to the treatment of patients with definitively diagnosed DIC with high DIC scores and high prognostic scores, such as SOFA and APACHE II. However, for patients only sus-



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Fig. 33.8 A three-dimensional chart showing the log-transformed relative hazard ratios with 95% confidence intervals (gray plate) for hospital mortality of the ISTH DIC scores and APACHE II scores with (blue plate) and without (pink plate) anticoagulant therapies. The red arrow indicates the reduction in hazard ratios at the most severe subset

in both scores. The result suggests that anticoagulant therapy may be beneficial in patients with DIC and a high disease severity. *APACHE II* Acute Physiology and Chronic Health Evaluation II, *DIC* disseminated intravascular coagulation, *ISTH* International Society on Thrombosis and Haemostasis. (Reprinted with permission [156])

pected of having DIC or with low DIC scores, the repeated calculation of the DIC score is necessary. Continuous or worsening of the coagulation score on the first day of sepsis was associated with an increased risk of MODS and mortality rate [160]. A significantly lower survival probability in patients with newly developed DIC and persistent DIC than in those without DIC or those whose DIC improved from days 0 to 3 after the diagnosis of sepsis was repeatedly confirmed [161, 162]. Odds ratios after adjusting for potential confounders of DIC for the association of DIC with the development of MODS and death were consistently higher on day 3 after the diagnosis of DIC than on day 0 [162]. The results of these studies support the importance of the repeated evaluation of DIC scores for making treatment decisions and predicting the outcome of the patients. Taken together, these findings suggest persistent or worsening DIC score is confirmed, then it is time to start DIC treatment.

33.8 Underlying Disorders

The ISTH proposed the concept of controlled and uncontrolled DIC [6]. The endothelial regulatory network is temporarily activated and overridden under condition of controlled DIC, and this event is quickly reversed once the underlying conditions are removed or treated, i.e., transfusion reaction or abruptio placentae. Uncontrolled DIC occurs when the regulatory network becomes insufficient (TFPI, antithrombin, protein C, thrombomodulin) or injured (endothelial cells), i.e., trauma and sepsis. As defined, controlled DIC can be resolved by the resolution of the underlying disorder; however, in uncontrolled DIC, simultaneous treatments of both DIC and the underlying disorders, such as trauma, is always required [1, 6, 163].

33.9 Substitution Therapy

Consumption coagulopathy recognized as thrombocytopenia, low fibrinogen levels, and a prolonged prothrombin time and APTT, is more

prominent in trauma-induced DIC than in septic DIC due to the synergistic effects of consumption, loss by critical bleeding, and effects of dilution. Hayakawa et al. [164] showed that the platelet counts, prothrombin time, APTT, and fibrinogen reached the critical thresholds for massive bleeding faster in DIC patients than in non-DIC patients during the first 24 h after trauma. Many studies focusing on trauma found that in addition to RBC, DIC patients more frequently needed the transfusion of platelet concentrates, fresh-frozen plasma (FFP), and fibrinogen concentrate than in non-DIC patients [13, 25, 117, 123, 164]. To stop both trauma-induced critical bleeding and DIC-evoked oozing-type bleeding, substitution therapy using platelet concentrate, FFP, or fibrinogen concentrate is required in DIC after trauma. The critical thresholds for initiating each type of substitution therapy are mentioned in the ISTH guidance [163].

Caution should be practiced when the prothrombin complex concentrate (PCC) is applied as substitution therapy [1, 163]. In addition to a lack of essential coagulation factors, such as FV, VIII, and FXIII, PCC does not contain any or contains a very small amount of anticoagulation factors, such as antithrombin, protein C, and protein S [1, 163]. As a result, PCC increases thrombin generation accompanied by thrombocytopenia and a prolonged prothrombin time, potentially inducing or aggravating thromboembolic complications and DIC [165–168]. A careful check of the constituents of PCC at each ICU is required.

33.9.1 Anticoagulants

33.9.1.1 Heparin

A recent trend in anticoagulant use for DIC is that anticoagulant factor concentrates is preferred to unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Thus far, no robust clinical study on heparin use for DIC showing an improvement of patient's outcome has been published. The ISTH guidance recommends a therapeutic dose of heparin be administered to DIC patients, preferring LMWH to UFH based on the results of a small randomized controlled trial [163, 169].

33.9.1.2 Anticoagulant Factor Concentrates

The ideal anticoagulant factor concentrates to use for the treatment of DIC has been controversial. After the withdrawal of activated protein C from the global market, we now have two anticoagulation factor concentrates available for use; antithrombin and recombinant human soluble thrombomodulin (rhsThrombomodulin) [170]. After the publication of the ISTH guidance recommending the administration of antithrombin or rhsThrombomodulin for DIC (potentially recommended, needs further evidence) [163], many valuable studies on these drugs have been published.

Antithrombin A systematic review and meta-analysis concluding that there was no evidence antithrombin improves the mortality of patients with sepsis or DIC included serious flaws in their analysis of the largest population of the KyberSept trial, due to the fact that in that analysis, they did not select DIC patients [146, 171, 172]. Post hoc analyses of the KyberSept trial showed that antithrombin improved the outcome without increasing bleeding side effects in patients with DIC at high risk of death and without concomitant use of heparin [149, 153, 159]. Although the KyberSept trial used an extremely high dose of antithrombin, evidences supporting a supplementary dose of antithrombin administration for septic DIC has been published. A supplementary dose of antithrombin improved the DIC score and doubled the DIC recovery rate without any risk of bleeding [173]. Using a nationwide database, Tagami et al. showed that antithrombin was associated with a significant reduction in mortality rates among DIC patients [174, 175]. In addition, a meta-analysis concerning antithrombin for sepsis-induced DIC repeatedly confirmed a significant reduction in the mortality rate [176]. Using antithrombin for DIC is promising, so a multinational prospective randomized trial concerning the efficacy of a supplementary dose of antithrombin for DIC needs to be conducted [176, 177].

rhsThrombomodulin A phase III randomized double-blind controlled trial showed the superiority of rhsThrombomodulin to heparin for

improving DIC and alleviating bleeding symptoms in patients with infection or hematological malignancies [178]. Following this trial, a phase IIb study restricting participants to those with sepsis and suspected DIC was conducted, which encourage us to conduct further trials on the rhsThrombomodulin in sepsis-associated coagulopathy including DIC [179]. This phase IIb study identified three factors that were associated with a reduced mortality among septic patient; the prothrombin time international normalized ratio (PTINR) >1.4, thrombocytopenia, and dysfunction in at least one organ. However, a phase III trial of rhsThrombomodulin failed to reduce the mortality in patients with sepsis-associated coagulopathy diagnosed with using above-mentioned three factors [180]. Post hoc analyses showed three issues likely associated with the negative results; concomitant heparin use, patients no longer meeting the inclusion criteria for platelet counts and PTINR at the starting point of the drug, and no stratification of the patients by thrombin generation levels [180, 181]. Subgroup analyses of the phase III trial after adjusting for these three factors showed a significant reduction in the mortality rates in rhsThrombomodulin group compared with the control group [180, 182–184]. The new terms “sepsis-associated coagulopathy” and “sepsis-induced coagulopathy” cooperating three items identified in phase IIb trial were established and rhsThrombomodulin therapy for patients who met these criteria showed a reduction in mortality [185]. Further study will need to be performed in order to confirm the positive effect of rhsThrombomodulin on these two coagulopathies and DIC.

33.9.2 Antifibrinolytics

Antifibrinolytic agents are contraindicated in DIC with the thrombotic phenotype [1, 163]. However, antifibrinolytics are considered for use in DIC with the fibrinolytic phenotype diagnosed at a very early stage of trauma and in cases with acute promyelocytic leukemia [1, 163]. The CRASH-2 trial showed a reduction in the risk of death in bleeding trauma patients who used

tranexamic acid within 3 h after injury [186, 187]. The coagulofibrinolytic changes in iTBI patients are the same as those in patients without brain injury, so, DIC immediately after iTBI also belongs to fibrinolytic phenotype [33, 131]. The CRASH-3 trial demonstrated significant reductions in head-injury-related death due to the administration of tranexamic acid, especially in patients with mild-to-moderate head injury and those who received early tranexamic acid treatment [188].

The CRASH-2 and CRASH-3 were not intended to include DIC patients; however, the mechanisms underlying the effects of tranexamic acid on the fibrinolytic systems and restricted effective timeframe within a few hours after injury support the notion that tranexamic acid may improve excessive bleeding in DIC patients with a fibrinolytic phenotype at very early stage of trauma and in those with iTBI.

33.9.3 Histones and NETs

Histones and NETs are promising targets for improving DIC, organ dysfunction, and the outcome. Some experimental studies have shown that anti-histone antibody ameliorated histone-induced IL-6 release, thrombin generation, endothelial injury, organ dysfunction, and survival probability [50, 76, 140]. rhesThrombomodulin binds to histones and was shown to improve histone-induced platelet aggregation and thrombocytopenia, microvascular thrombosis, organ dysfunction, and the survival probability [84]. Nonanticoagulant heparin prevented the cytotoxic effects of histones and improved the mortality rates in mouse model of sepsis and sterile infection [189]. It further attenuated the histone-induced pro-inflammatory cytokines (IL-6, IL-8) production, tissue factor generation, and C3a formation in a whole blood model [190]. Peptidylarginine deiminase 4 (PAD-4) is a key protein for NETs formation (NETosis) as a citrullinating enzyme of arginine residues of histones

that results in chromatin decondensation and the release of neutrophil DNA (NETs) [191]. In addition, PAD4 is now known to regulate pathological thrombosis [191]. Therefore, PAD4 inhibitors prevent the formation of NETs and thrombosis. Already formed NETs DNA could be degraded using DNase. Aside from rhesThrombomodulin, these drugs are still in the experimental phase; however, their potential efficacy is promising for DIC treatment [78, 191].

33.10 Conclusions

DIC is defined as dysregulated inflammatory and coagulofibrinolytic responses to the insults and is deeply involved in the outcome of critically ill patients due to the development of bleeding and MODS. DIC involves systemic thrombin generation, insufficient anticoagulation pathways, and increased fibrinolysis (followed by its impairment) in association with endothelial injury. DAMPs, especially histones released from injured cells and activated neutrophil-formed NETs containing neutrophil DNA, histones, and elastase are considered the main pathomechanisms involved in DIC. Histones and NETs synergistically induce systemic inflammation, platelet and coagulation activation, dysfunction of anticoagulant systems, and inhibition of fibrinolysis, leading to microvascular thrombosis. Histone-induced direct cellular injury, including that of endothelial cells, as well as the reduction in oxygen delivery due to microvascular thrombosis give rise to MODS. Platelet dysfunction, consumption coagulopathy, and hyperfibrin(ogen)olysis induce oozing-type of bleeding. DIC can be diagnosed using a diagnostic scoring system. Definitively diagnosed DIC with a high disease severity and persistent or worsening DIC is the true target of the treatment with anticoagulant factor concentrates in trauma patients admitted to the ICU.

Even today, it is important to keep in mind the fact that DIC equals a sign that “Death Is Coming” [192].

Key Concept

- DIC, defined as dysregulated inflammatory and coagulofibrinolytic responses to an insult and known as thrombohemorrhagic disorder, markedly affects a patient's outcome due to microvascular thrombosis-induced organ dysfunction and critical bleeding.

Take Home Messages

- Trauma is a leading cause of DIC.
- Bidirectional interplays among innate immunity, inflammation, and coagulation play important roles in the pathophysiology of DIC.
- Histones, as well as NETs involved in inflammation, activation of coagulation, impairment of anticoagulation controls, and the inhibition of fibrinolysis, lead to microvascular thrombosis and endothelial cell injury.
- Microvascular thrombosis- and endothelial cell injury-caused MODS and consumption coagulopathy-induced critical bleeding affects a patient's outcome.
- To improve a patient's outcome, the simultaneous treatments of trauma-itself, DIC, and MODS is necessary.

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