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Mechanisms and management of the coagulopathy of trauma and sepsis: trauma-induced coagulopathy, sepsis-induced coagulopathy, and disseminated intravascular coagulation

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Abstract

Disseminated intravascular coagulation can occur due to different causes but commonly following sepsis. Trauma-induced coagulopathy (TIC) occurs on hospital arrival in approximately 25% of seriously injured patients who initially presents with impaired hemostasis and a bleeding phenotype that can later progress to a prothrombotic phase. Following traumatic injury, ineffective hemostasis is driven by massive blood loss, tissue damage, and hyperfibrinolysis. This initial impaired hemostasis continues until surgical or other management strategies not only to stop the causes of hemorrhage but also progresses to a prothrombotic and hypofibrinolytic state, also termed fibrinolytic shutdown. Prothrombotic progression is also promoted by inflammatory mediator release, endothelial injury, and platelet dysregulation, which is commonly seen in sepsis with increased mortality. Unlike TIC, the early phase of sepsis is frequently complicated by multiorgan dysfunction described as sepsis-induced coagulopathy (SIC) that lacks a hemorrhagic phase. The phenotypes of SIC and TIC are different, especially in their initial presentations; however, patients who survive TIC may also develop subsequent infections and potentially sepsis and SIC. Although the pathophysiology of SIC and TIC are different, endothelial injury, dysregulated fibrinolysis, and coagulation abnormalities are common. Management includes treatment of the underlying cause, tissue injury vs infection is critical, and supportive therapies, such as hemostatic resuscitation and circulatory support are essential, and adjunct therapies are recommended in guidelines. Based on clinical studies and certain guidelines, additional therapies include tranexamic acid in the limited timing of initial traumatic injury and anticoagulants, such as antithrombin and recombinant thrombomodulin in disseminated intravascular coagulation.

KEYWORDS
anticoagulant, coagulopathy, disseminated intravascular coagulation, endothelial cell, fibrinolysis

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1 | INTRODUCTION

Hemostasis is an essential response to various insults, and coagulation is critical to host defense systems. Following infection, cellular injury, and other pathologic responses, a thromboinflammation response occurs as part of host surveillance mechanisms. In the most extreme type, disseminated intravascular coagulation (DIC) can occur, a response defined as systemic coagulation activation with impaired hemostasis and/or organ dysfunction [1]. The activation of coagulation commonly occurs in DIC, and a corresponding fibrinolytic response can also occur depending on multiple factors. As a result, DIC has been classified as hypofibrinolytic, hyperfibrinolytic type, and balanced in their pathologic responses [2]. From a clinical perspective, DIC is commonly considered as either a thrombotic or hemorrhagic phenotype, and the clinical presentation is determined by the balance between a procoagulant and fibrinolytic response that can change rapidly over time. Of note, since the clinical manifestations vary depending on underlying conditions, it is important to follow the clinical manifestation over time of individual cases. As a reminder, DIC is a laboratory-based pathologic diagnosis due to a specific underlying cause and commonly presents clinically with contrastive findings, in which endothelial injury, a hallmark of the condition, facilitates the simultaneous coexistence of thrombosis and bleeding (Figure 1) [3]. Historically, the concept of DIC has long been misunderstood because DIC is an end-stage coagulopathy with high morbidity and mortality [4]. However, the initial presentation of early-stage DIC may be a reversible condition based on rapid and appropriate management, especially in the case of acute infections and sepsis.

Important obstacles in DIC management include an inappropriate understanding of the heterogenicity of the underlying causes, difficulty in the timely initiation of the treatment, and the lack of specific therapeutic agents [5,6]. These complicated factors often puzzle clinicians, and many think DIC still stands for "diffuse international confusion." This review will examine the approaches to the different clinical manifestations of trauma- and sepsis-induced coagulopathy (SIC) and phenotypes of DIC, including hemorrhagic and thrombotic types.

2 | A CASE PRESENTATION

A 42-year-old man was brought to the emergency room after a motor vehicle accident. On arrival, the heart rate was 130 beats per minute, the systolic blood pressure was 65 mmHg, and SpO_2 was <90% with respiratory support. The body temperature was 35.2 °C, and the pH was 7.12 with a negative 11.2 mmol/L base excess on arterial blood gas. An intravenous catheter was placed, blood component therapy administration was started, additional laboratory tests were sent, and a focused assessment sonography for trauma revealed hemoperitoneum in the pelvic space and a right-sided hemothorax. The radiographs showed pneumothorax, pulmonary contusion with multiple rib fractures, and unstable pelvic fracture with massive bleeding. The coagulation tests showed prothrombin time (PT) prolongation of 7 sec, D-dimer of 10.8 μg/mL, platelet count of 55×10^9/L, and fibrinogen level of 0.9 g/L (overt DIC score = 7 points). Within 3 hours after the accident, 1.0 g of tranexamic acid (TXA) was administered intravenously, followed by another 1.0 g infused over 8 hours. Laparotomy was performed for hypotension, and the finding of a positive focused assessment sonography for trauma result. External fixation and preperitoneal pelvic packing were performed for the unstable pelvic fracture, but the bleeding continued during the surgical procedure. The clinical trauma coagulopathy score was IVb [7]. Volume resuscitation using a massive transfusion protocol (red blood cell [RBC]:fresh frozen plasma [FFP]:platelet ratio of 2:1:1, and fibrinogen concentrate [>25 mg/kg]) was administered to achieve hemoglobin level of >7.0 g/dL, platelet count of $> 50 \times 10^9$/L, PT ratio of <1.5, and fibrinogen of 1.5 to 2.0 g/L.

Postoperatively, on day 6, the patient spiked fever of >39.0 °C with decreased consciousness, and systolic blood pressure was 65 mmHg. Norepinephrine was administered to keep the mean arterial

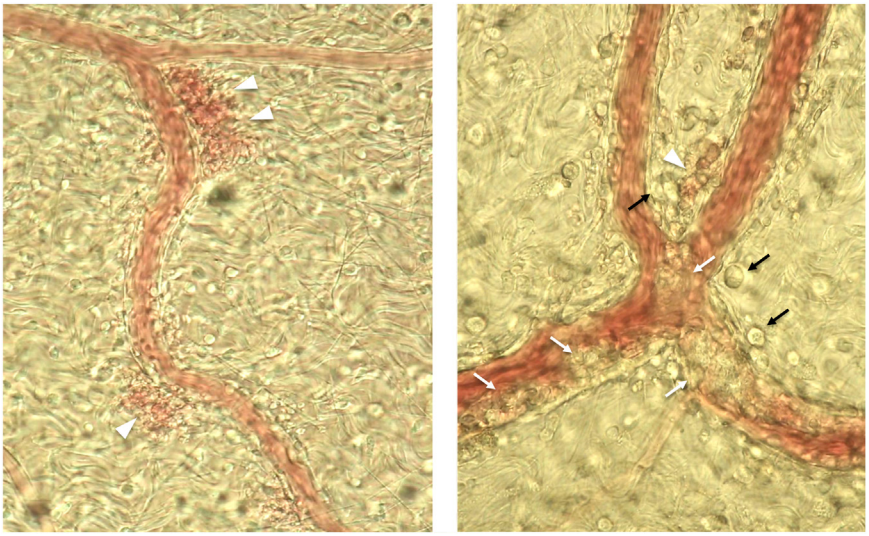

FIGURE 1 Bleeding and thrombus in the microcirculation in a sepsis model of rat. Rat mesenteric microcirculation was observed under the intravital microscope after lipopolysaccharide injection. At 3 hours, microbleeding was observed (left panel, white arrowheads). In the right panel, round, stiff leukocytes adhered to the unsmooth and swollen endothelial cells and formed microthrombi (white arrows). The leukocytes transmigrated to the extravascular space (black arrows). The extravasation of the red blood cells was also seen in this panel (white arrowhead). Along with these changes, the blood flow gradually decreased.

pressure of >65 mmHg, blood cultures, sputum, and urine cultures were obtained, and empirical antibiotic coverage for gram-positive and gram-negative coverage was initiated for the patient. Laboratory test results showed a white blood cell count of 4000/μL, C-reactive protein of 18.9 mg/dL, total bilirubin of 2.8 mg/dL, creatinine of 1.19 mg/dL, lactate of 4.2 mmol/L, PT-international normalized ratio (INR) of 1.86, D-dimer of 5.8 μg/mL, antithrombin activity of 45%, and platelet count of 50 × 10^9/L. The total sequential organ failure assessment score was 9, and the SIC score was 6 (overt DIC score = 4). No clinically significant bleeding was observed, and antithrombin and recombinant thrombomodulin were administered based on Japanese guidelines for the treatment of DIC [8]. After 4 days of sequential treatments, the clinical condition and laboratory tests returned to almost normal status, and the patient was moved to a general ward (Figure 2).

3 | TRAUMA-INDUCED COAGULOPATHY AND SIC

DIC can occur due to diseases and conditions that include sepsis, trauma, hematologic malignancy, solid cancer, obstetrical catastrophes, severe hepatic failure, toxins, and shock [1]. Among these, advances in understanding the pathophysiology of sepsis and trauma have played critical roles in managing DIC. In sepsis-associated DIC, a timely diagnosis is important for success in the treatment, including early antibiotic therapy to treat the underlying cause, as late-phase DIC is resistant to treatment and may not be reversible. Thus, the detection of the early phase of DIC in patients with sepsis has been emphasized and categorized as SIC [9] (Table 1). Following major trauma, severe and uncontrollable bleeding can appear, and this early-phase trauma-associated coagulopathy is termed trauma-induced coagulopathy (TIC) [10]. Although both TIC and SIC can be consistent with the diagnostic criteria of overt DIC, the phenotype of the initial fibrinolytic phase of TIC (early TIC) is different from SIC [11]. Trauma patients who survive the initial TIC may develop a thrombotic phenotype in later stages (late TIC) that manifests multiple organ failure similar to SIC [10], and it may also manifest with macrovascular thrombotic complications, such as deep vein thrombosis/pulmonary embolism. In such cases, the activation of coagulation triggers unbalanced fibrinolysis, and impaired endothelial function and subsequent microthrombosis play major roles in the development of organ dysfunction. However, the pathogenic significance of activated coagulation, unbalanced fibrinolysis, and endothelial damage frequently differs in TIC and SIC [12]. Discrepancies have long existed among researchers, but a recent consensus with regard to the similarities and differences between SIC and TIC was reported by the International Society on Thrombosis and Haemostasis (ISTH) in 2020 [10].

4 | ACTIVATION IN COAGULATION

The systemic coagulation activation leads to microcirculatory thrombosis, the pathophysiologic response of DIC; however, the underlying mechanisms are far more complex. Although different disease states can lead to DIC, the representative pathways that initiate SIC include

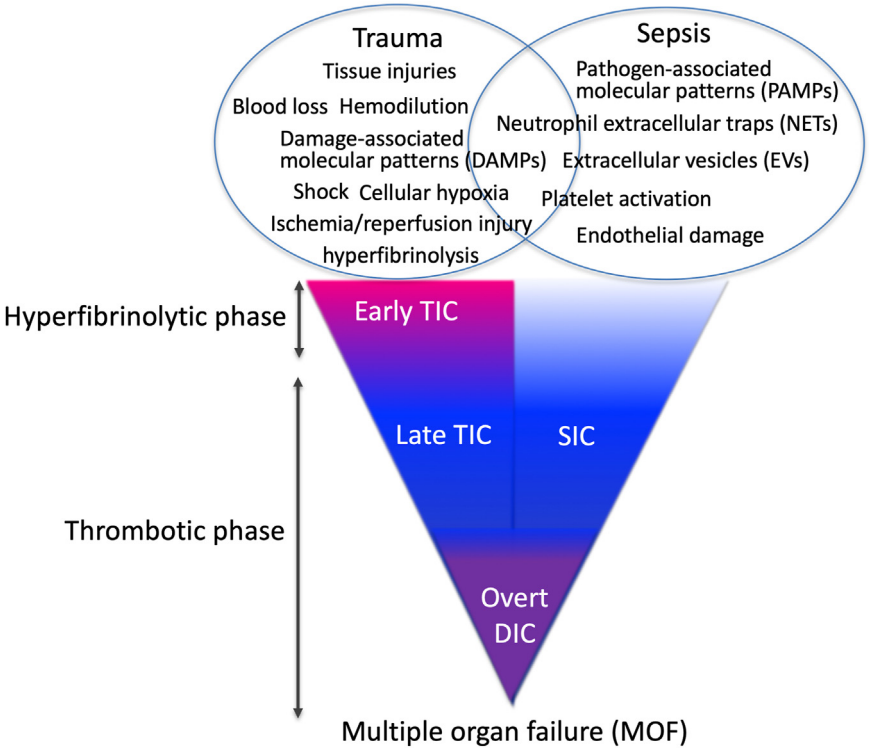

FIGURE 2 Clinical course of the case. A 42-year-old man had multiple trauma caused by a car accident. Respiratory failure and hemorrhagic shock were recognized at presentation. Respiratory support and fluid resuscitation were initiated followed by blood transfusion. The patient was diagnosed trauma-induced coagulopathy due to impaired hemostasis. Pelvic fixation and pelvic packing were performed successfully after transfusion and antifibrinolytic therapy. On postoperative day 6, patient presented with high fever and shivering suddenly and fell into shock on the next day. Sepsis-induced coagulopathy score was 6, and anticoagulant therapy was initiated along with antibiotic therapy. Sepsis-induced coagulopathy was resolved on day 10, and the patient was moved to a general ward. DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; TXA, tranexamic acid.

TABLE 1 ISTH overt DIC and SIC scoring systems.

Item	Score	ISTH overt DIC Range	ISTH SIC Range
Platelet count ($\times 10^9$/L)	2	<50	<100
	1	≧50, <100	≧100, <150
FDP (D-dimer)	3	Strong increase	–
	2	Moderate increase	–
	1	–	–
Prothrombin time	2	≧6 sec	>1.4 (PT-INR)
	1	≧3 sec, <6 sec	>1.2, ≦1.4 (PT-INR)
Fibrinogen (g/mL)	1	<100	–
SOFA score	2	–	≧2
	1	–	1
Total score for DIC or SIC[a]		≧5	≧4

DIC, disseminated intravascular coagulation; FDP, fibrinogen degradation product; JAAM, Japanese Society for Acute Medicine; ISTH, International Society on Thrombosis and Haemostasis; SIC, Sepsis-induced coagulopathy; SIRS, Systemic Inflammatory Response Syndrome; SOFA, sequential organ failure assessment.

[a] Total SOFA score is the sum of 4 items (respiratory SOFA, cardiovascular SOFA, hepatic SOFA, and renal SOFA).

cell-based and humoral-based mechanisms [13,14]. Pathogen-associated molecular patterns and the host responses against infection are critical factors in the pathogenesis of coagulation activation in sepsis. Tissue factor expressed on macrophages, monocytes, vascular endothelial cells, platelets, and extracellular vesicles released from related cells is thought to trigger extrinsic pathway activation [15]. In addition, phosphatidylserine residues expressed on cell membranes on various cell types, as well as microvesicles, activate the intrinsic coagulation cascade [16], with activated or damaged leukocytes releasing neutrophil extracellular traps that accelerate procoagulant reactions [17]. Damage-associated molecular patterns (DAMPs) released from the host cells, including DNA, histones, and high-mobility group box 1, also contribute to the progression of coagulopathy. Activation of cellular components that include platelets, RBCs, and endothelial cells also participate in the prothrombotic processes [13]. As a result, pathogen-associated molecular patterns, DAMPs, neutrophil extracellular traps, activated immune cells, and damaged host cells propagate prothrombotic and proinflammatory responses in SIC and coagulopathies from other causes [18].

In TIC, tissue injury and hemorrhagic shock drive sterile inflammation (Figure 3). These noninfectious injury pathways are dependent on inflammatory mediators that are also important in SIC [19]. However, tissue injury is an important distinguishing feature of TIC and likely activates sterile-injury pathways to produce the hyperfibrinolytic phenotype. Tissue factor and other phospholipids released following brain injury trigger coagulopathy and fibrinolysis, a response that is amplified in the setting of polytrauma and hemorrhage. Tissue hypoxia is another factor that can induce coagulopathy, and recently, shock due to cardiac arrest and reperfusion injury has also been added to the list of underlying conditions [20] (Table 2).

5 | IMPAIRED FIBRINOLYTIC SYSTEM

After major trauma, time-dependent changes in coagulation and fibrinolysis also occur. The release of tissue plasminogen activator from endothelial cells may be involved in the initial activation of fibrinolysis in response to a burst of thrombin and fibrin generation. This fibrinolytic phase ends within several hours of the plasminogen activator inhibitor-1 (PAI-1) production by endothelial cells and possibly platelets. This dynamic change is named "fibrinolytic shutdown" [21] that may rapidly occur in 40% to 50% of patients, despite arriving at the hospital within an hour after injury [22]. Roughly one-fourth of trauma patients have evidence of prior fibrinolytic activation, but only 7% have active ongoing fibrinolysis at the time of the initial blood sampling [23]. Alternative hypotheses to explain the derangement in fibrinolysis include the presence of an occult hyperfibrinolytic state that essentially appears as "shutdown" as a consequence of limitations of diagnostic testing [24,25]. This occult hyperfibrinolytic state has been reported to be mediated by S100A10, a cell surface plasminogen receptor [24]. Fibrinolytic activation and its suppression are not TIC-specific but occur less frequently in patients with sepsis, because the initial fibrinolytic phase has passed by the time the patient arrives at the hospital [23]. As a result, biphasic changes in fibrinolysis are recognized in TIC, and only a late suppressive phase would be detected in SIC. The fibrinolysis-predominant phase of early TIC usually persists for only several hours, and the subsequent fibrinolysis-suppressed phase is sustained in most patients with sepsis.

Trauma patients with fibrinolytic shutdown who recover at 24 hours have improved outcomes compared with those with persistent fibrinolytic inhibition, the finding also as noted in SIC [21]. The

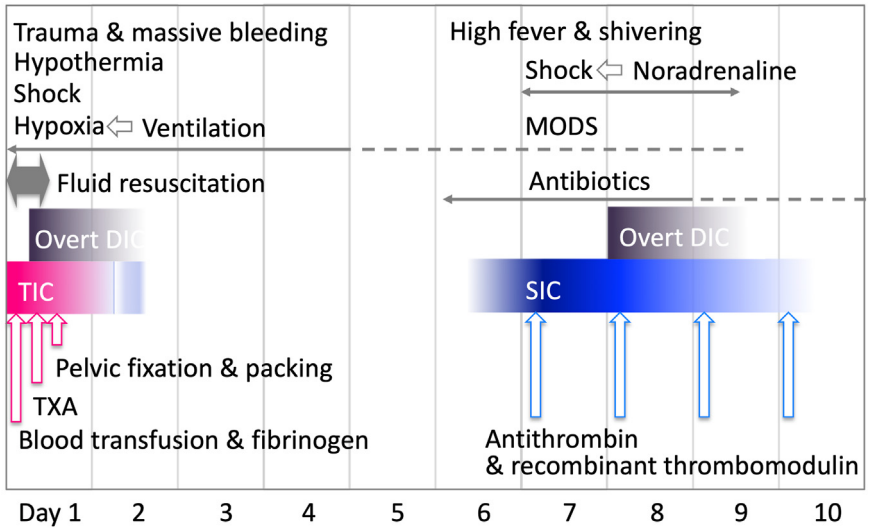

FIGURE 3 Time courses of trauma-induced coagulopathy and sepsis-induced coagulopathy. Tissue damage-induced activated coagulation, massive blood loss, tissue malcirculation, and hemodilution are the important factors of impaired hemostasis seen in early trauma-induced coagulopathy (TIC). In contrast, such a phase is rarely seen in sepsis-induced coagulopathy. Inflammatory and procoagulant reactions play critical roles in the development of widespread microthrombosis. Hemorrhagic early TIC turns to thrombotic late TIC and progresses to overt disseminated intravascular coagulation.

suppression of fibrinolysis is considered to be a part of the natural host response to systemic infection, and innate immune responses interplay with the coagulation system. This temporal up-regulation, followed by sudden over-suppression in fibrinolysis, is caused mainly by the derangement of the endothelial cells following tissue injury and shock.

Monitoring fibrinolysis in clinical practice is problematic because of the lack of optimal tests. Fibrin/fibrinogen degradation products (FDPs) are commonly measured, but they are affected by both coagulation and fibrinolytic activities. Although FDPs, including D-dimer, are elevated, they do not correlate well with severity [26]. In addition, FDPs have long half-lives, and their rise may not account for the concomitant suppression of fibrinolysis occurring by PAI-1. Plasmin-antiplasmin complex and PAI-1 are more specific biomarkers of fibrinolysis, but measurements are not readily obtainable in most clinical settings. Viscoelastic testing using point-of-care devices, including thromboelastography and rotational thromboelastography is applicable for real-time detection of fibrinolysis [27] and are used extensively in the trauma patient. Accumulated evidence showed the potential efficacy of viscoelastic testing following trauma on goal-directed therapy for directing hemostatic management and resuscitation [28,29], although some concern for lack of sensitivity for the detection of fibrinolysis persists [25].

6 | ANTICOAGULANT SYSTEMS

Endothelial dysfunction and derangement of the physiological anticoagulants are the hallmarks of both SIC and TIC. Under physiological conditions, thrombogenicity and hemostasis are balanced by physiological anticoagulant proteins, including antithrombin, protein C, protein S, and thrombomodulin. Among these, antithrombin is the most abundant and most important anticoagulant that inhibits clot formation [30]. Vascular endothelial cells also play pivotal roles in maintaining hemostatic balance with their antithrombotic mediators, such as tissue factor pathway inhibitor, nitric oxide, and prostacyclin. Following injury, however, they can also express prothrombotic factors, including tissue factor, von Willebrand factor, and adhesion molecules that facilitate leukocyte and platelet adhesion. The glycocalyx, a gel-like layer composed of proteoglycans and

TABLE 2 The hemostatic changes in TIC and SIC.

Item	Early TIC	Late TIC	SIC
Coagulation	↑	↑	↑↑
Anticoagulation	↑?	↓	↓↓
Fibrinolysis	↑	↓	↓↓
Platelet function	↓?	↑	↑↑
Endothelium /glycocalyx	Damaged and contributes to anticoagulation?	Damaged and endothelial surface becomes procoagulant	Damaged and endothelial surface becomes procoagulant
Microthrombus	−	+	+
Phenotype	Bleeding-dominant	Prothrombotic and development of organ dysfunction	Prothrombotic and development of organ dysfunction

TIC, trauma-induced coagulopathy; SIC, sepsis-induced coagulopathy.

glycosaminoglycan side chains on the cell surface, exerts critical antithrombotic effects by binding to antithrombin [31]. Endothelial cells also balance fibrinolysis by producing t-PA and PAI-1 [32].

Antithrombotic activity is significantly suppressed in SIC, and the prognostic value of antithrombin activity is reported to be more important than that of global coagulation tests, such as platelet count, PT, and plasma levels of FDP and D-dimer [33]. Similar to SIC, low-antithrombin activity is associated with an increased risk of coagulopathy and death in trauma [34]. Severe antithrombin deficiency has recently been implicated in post-trauma deep vein thrombosis and a lack of response to thromboprophylaxis with low molecular weight heparin [35]. Additional factors, such as blood loss, dilution, and increased permeability, can reduce antithrombin, but the changes in anticoagulant function are complex. In early TIC, thrombomodulin is shed into the circulating blood and potentially suppresses coagulation through the activation of protein C [10,36]. At the same time, thrombomodulin on the endothelial surface is significantly decreased, which may also affect hemostatic balance in TIC [10,37]. Thrombin generation is further increased following tissue damage, hypoperfusion, and shock liver [38]. In late TIC, anticoagulants, such as antithrombin and protein C, are decreased for several days following massive bleeding, consumption, decreased production, and extravasation [39]. The decrease of protein C and thrombomodulin in SIC is thought to be due to the depressed production and extravasation [40] that result in decreased antithrombogenicity in the vasculature. Accordingly, further discussion to clarify the relationship between endothelial damage and pro- and anticoagulant properties in SIC and TIC follows.

7 | DEFINITION OF TIC

Coagulopathy is defined as an acquired condition characterized by activation of coagulation accompanied by altered fibrinolysis, from increased to suppressed levels, and when these changes occur systemically, that condition satisfies the definition of DIC. In this meaning, coagulopathy is the nonovert DIC. This early DIC can be a complication of various diseases and potentially develop into overt DIC [41]. Thus, multiple disease states can cause DIC, and the flows from SIC to overt DIC have been most extensively studied in sepsis.

Sepsis was redefined in 2016 as "life-threatening organ dysfunction caused by a dysregulated host response to infection [42]," and the Scientific and Standardization Committee on DIC of the ISTH defined SIC as "infection-induced organ dysfunction and coagulopathy," and published the diagnostic criteria which are composed of platelet count, PT-INR, and sequential organ failure assessment score [43,44]. Although an official definition has not been determined, TIC can be defined as "trauma-induced activation in coagulation, potentially progressing from impaired hemostasis to excessive thrombosis, accompanied by unbalanced fibrinolysis." Diagnostic criteria for TIC have also not been determined yet, but the symptom-based clinical diagnosis and urgent treatment should precede the laboratory test-based diagnosis. At least one clinical scoring system has been generated and utilized for quantification of clinical TIC severity as part of randomized clinical trials [7]. On the other hand, in patients with sepsis who may develop DIC, early diagnosis using SIC diagnostic criteria is helpful in judging the disease severity, and also for initiating anticoagulant therapy [43].

8 | PROPOSED MANAGEMENT

8.1 | Initial resuscitation and antifibrinolytic therapy

Extensive tissue injury with massive bleeding is a major problem in trauma patients. The latest version of the "European guideline on management of major bleeding and coagulopathy following trauma" recommends the use of either FFP plus packed RBC at a ratio of at least 1:2, or of fibrinogen concentrate plus packed RBC, for resuscitation, indicating the importance of supplementation of coagulation factors [45]. At the same time, this guideline cautions against the aggressive use of FFP and fibrinogen concentrate because of the increased hemostatic events, implying that both bleeding and thrombotic events can occur concurrently in trauma patients. The guidelines also recommend the use of TXA as soon as possible, at least within 3 hours of injury in patients with bleeding or at the risk of significant hemorrhage. Prehospital administration of TXA to severely injured patients has been associated with a survival benefit [46]. Several studies have suggested the use of viscoelastic testing to determine the treatment timing and to guide resuscitation, but the European guidelines do not recommend waiting for the results of the viscoelastic testing, and compared with the US perspective, less concern regarding the role of the fibrinolytic shutdown. A *post hoc* analysis of Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH)-2 (a randomized controlled trial and economic evaluation of the effects of TXA on death, vascular occlusive events, and transfusion requirement in bleeding trauma patients) revealed that the danger associated with TXA use was related to its administration later than 3 hours after injury [47]. In patients with TIC, there is a concern that giving TXA empirically to patients without evidence of excessive fibrinolysis may cause early fibrinolysis resistance and increased mortality [48], although this has not been studied in a randomized fashion and the overwhelming amount of evidence from randomized controlled studies supports the use of TXA to reduce mortality. In comparison to TIC, the fibrinolytic phase is rarely seen, and the incidence of bleeding is lower in SIC; therefore, an antifibrinolytic agent is not routinely administered in SIC.

8.2 | Anticoagulant therapy

Since thrombin is a critical mediator of coagulopathy in TIC, maintaining physiological antithrombin levels could be considered as a rational approach, and the use of plasma in the initial therapy for bleeding control is considered important for maintaining hemostatic balance and preventing endothelial injury. However, in some

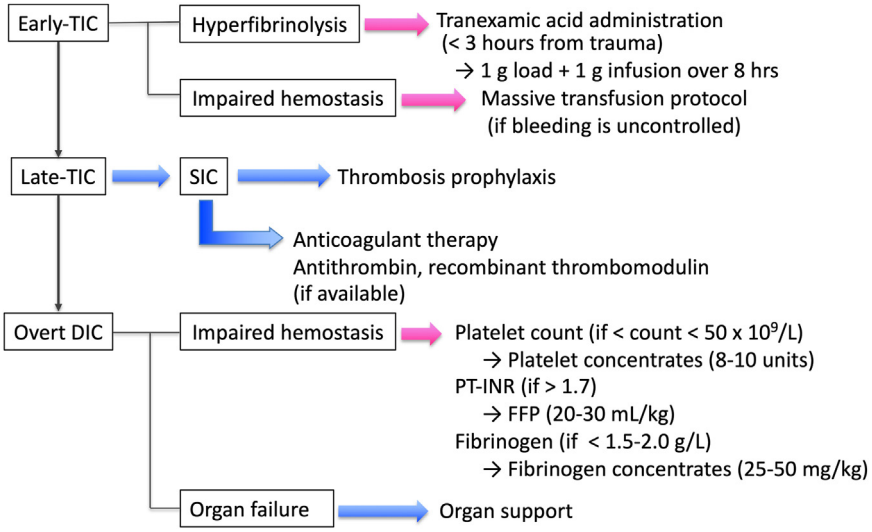

FIGURE 4 Treatment for disseminated intravascular coagulation (DIC). The treatment for DIC is different depending on the phases. For early trauma-induced coagulopathy, the use of tranexamic acid is considered if the time is within 3 hours after the accident, and blood transfusion is performed by following the massive fusion protocol. For late trauma-induced coagulopathy and sepsis-induced coagulopathy, thrombus prophylaxis is recommended. Anticoagulant therapy for sepsis-induced coagulopathy is recommended in Japanese guidelines. For the consumptive coagulopathy in overt DIC, supplemental therapy is performed. FFP, fresh frozen plasma; PT-INR, prothrombin time-international normalized ratio.

countries, with the use of prothrombin complex concentrates, decreased antithrombin may be insufficient to firmly regulate local hemostasis and counter enhanced systemic thrombin generation in trauma [49]. Decreased antithrombin activity is an important determinant of thrombin generation, reflected by increase in the levels of soluble fibrin, prothrombin fragment$_{1.2}$, thrombin-antithrombin complex, and D-dimer in trauma [39,50]. A multicenter, prospective study on trauma patients with an injury severity score ≥16 revealed the group with low-antithrombin activity at hospital presentation (n = 75) was associated with higher prevalence of shock, transfusion requirements, and in-hospital mortality compared with normal antithrombin activity group (n = 200). Higher DIC scores and more severe organ dysfunction were also observed in the low-antithrombin activity group [51]. Although it is not direct evidence for TIC, Vincent et al. [35] reported *ex vivo* supplementation of antithrombin to 150% was associated with the highest prophylactic activated antifactor X levels and reductions in thrombin generation. In addition, it is important for modulating inflammation. Furthermore, antithrombin may be required for the effective use of low molecular weight heparin for post-trauma thromboprophylaxis and to prevent thrombosis in late TIC [35].

Similar to major trauma, antithrombin levels decrease dramatically in sepsis, and the level correlates to disease severity. Since antithrombin is the most abundant physiological anticoagulant, antithrombin is expected to be most important to counterbalance the excess coagulation. Therefore, the efficacy of antithrombin supplementation in septic DIC has been repeatedly examined, and initial randomized controlled studies have shown beneficial results. However, the largest randomized controlled study namely KyberSept trial failed to demonstrate a survival benefit. Moreover, it was shown that antithrombin increased the bleeding adverse events and is rather harmful if it is used concomitantly with heparin for patients with sepsis without coagulation disorder [36]. Meanwhile, the subanalysis of the KyberSept trial suggested improved mortality when antithrombin is used for patients with sepsis and DIC without concomitant heparin [52]. Based on these findings, the Japanese guidelines for sepsis management recommend the use of antithrombin for patients with DIC [8]. A large-scale cohort study constructed >8000 cases using the Japanese Diagnosis Procedure Combination inpatient database has demonstrated the decreased mortality of pneumonia-induced DIC (propensity-matched, adjusted odds ratio: 0.85; 95% CI, 0.75-0.97) [53]. However, there is as yet no international consensus because of the lack of robust evidence.

Another option is the use of recombinant thrombomodulin, and its effect was examined in a multinational, randomized, controlled phase III trial in patients with SIC (not exactly the same entity). The 28-day mortality improved by 2.6% (26.8% vs 29.4%; relative risk, 0.92) in a total of 800 patients, although the difference in the mortality rates was not statistically significant. It was also reported from this trial that >20% of the patients recovered before the initiation of the treatment, and a subgroup analysis conducted on the patients who fulfilled the entry criteria at baseline revealed a reduction of mortality by 5.4% [54]. In addition, a phase IIb randomized trial enrolled 750 patients also showed nonsignificant but lower mortality (17.8% vs 21.6%) [55]. Other smaller studies consistently demonstrated a favorable effect without increased bleeding, and the Japanese guidelines for sepsis management recommend the use of thrombomodulin for patients with DIC [8]. Although the difference was still small, it should be remembered that a 1.5% difference (14.5% vs 16.0%; relative risk, 0.91) was noted in CRASH-2 [56]. It is also notable that all randomized controlled studies consistently showed the favorable effects of recombinant thrombomodulin. Recombinant thrombomodulin may also have a future role in late TIC management (Figure 4).

8.3 | Endothelial protection

During sepsis and septic shock, the endothelial glycocalyx is disrupted with an acquired deficiency of the protective regulator Heparanase-2. While FFP could bring the protective plasma proteins consumed during sepsis, therapeutic plasma exchange (TPE) might, in addition,

remove deleterious components shed from activated endothelial glycocalyx that serve as injurious DAMPs. In 20 patients with sepsis receiving TPE, Stahl et al. [57] have thus shown that a single TPE against FFP allowed removal of potentially injurious endothelial glycocalyx degradation products and partially attenuated Heparanase-2 deficiency. Interestingly, the same team has also shown that early plasma exchange reduced the imbalance between pro and anticoagulant factors that leads to DIC [58]. This could, therefore, improve subsequent organ failure, DIC, and the prognosis of the patients. These results are consistent with another small trial in which early use of a combination of FFP, low-dose heparin, and TXA in children with severe sepsis/septic shock in the "window of opportunity" before the development of overt DIC was associated with a better outcome to survival and prevention of developing overt DIC, with no increase in bleeding. Finally, in a randomized controlled trial including 112 patients with sepsis-associated DIC were randomly divided into the TPE group (n = 40), the heparin group (n = 36), and the sham control group (n = 36), Weng et al. [59] showed that TPE improved coagulation function and endothelial function, and thus improved patient outcome.

In the setting of trauma, multiple resuscitation strategies have been shown to reduce endothelial injury markers. Trauma is consistently associated with the shedding of the glycocalyx, although it remains unknown whether this is a marker of injury severity or a critical mechanistic component that leads to endothelial permeability and organ injury. Glycocalyx degradation has been linked to hypocoagulation through the release of endogenous heparins [60,61], and as such, preservation of an intact glycocalyx is thought to reduce manifestations of TIC. Expression of syndecan-1 in circulation following injury has been strongly linked to morbidity and mortality in trauma patients [62,63], with direct links to key phenotypes of TIC, including hyperfibrinolysis. Numerous strategies (steroids, protease inhibitors, and heparins) to restore the glycocalyx that have been studied in other disease states (COVID-19 and sepsis) remain unstudied or unproven in trauma. The best resuscitation strategy for reducing endothelial injury appears to be balanced hemostatic resuscitation, including early administration of plasma. Hierarchical clustering analysis of biomarkers of immune response and endothelial injury have shown that prehospital plasma can reduce levels of syndecan-1 and other endothelial injury markers following injury, and this reduction is associated with an improvement in mortality [64]. Finally, novel, endothelial targeted strategies, such as the use of recombinant ADAMTS-13, show clinical promise in treating trauma-associated endothelial injury and have been shown in preclinical models to reduce endothelial injury and glycocalyx shedding [65,66].

9 | SUMMARY

Although considerable gaps in the pathophysiology and phenotype between TIC and SIC, the systemic activation and endothelial damage, the essence of DIC, underlie both conditions. TIC has unique features characterized by initial major hemostatic impairment along with hyperfibrinolysis leading to inadequate hemostasis. The late-phase TIC shares feature represented by organ dysfunction and thrombotic tendency with SIC. There is now a consensus that the pathways of TIC and SIC, at least partially overlap but are not completely the same. For example, severe bleeding, often seen in major trauma, is not common in sepsis. On the other hand, organ dysfunction is the hallmark of SIC, which also becomes common in the late TIC. Although antithrombin and recombinant thrombomodulin are promising anticoagulants for SIC, the effects have not been examined in the late TIC because of the less prevalence. In summary, although the phenotypes are considerably different, the pathogeneses have overlapping characteristics. Sterile and nonsterile tissue injuries activate coagulation systemically through various mechanisms, and thrombin is the key factor in both conditions. Subsequent endothelial damage, impaired platelet function, and dysregulated fibrinolysis further accelerate tissue ischemia, eventually resulting in life-threatening organ dysfunction and DIC.

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AUTHOR CONTRIBUTIONS

T.I. and J. H.L. wrote the draft, M.D.N. and J.H. reviewed and revised the manuscript.

DECLARATION OF COMPETING INTERESTS

T.I. participated on advisory boards of Japan Blood Products Organization, Asahi Kasei Pharmaceuticals, and Toray Medical. J.H. has received honoraria from Diagnostica Stago, Pfizer PFE France and Sanofi Aventis France, MSD, Shionogi, and Inotrem. M.D.N. serves on the scientific advisory board for Haima Therapeutics, has received honoraria from Haemonetics, CSL Behring, and Takeda, and received research funding from Haemonetics and Instrumentation Laboratories. J.H.L. serves on the Steering or Advisory Committees for Instrumentation Laboratories, Merck, Octapharma.

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