journal of
thrombosis and haemostasis

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Journal:	*Journal of Thrombosis and Haemostasis*
Manuscript ID	JTH-2019-00812.R1
Manuscript Type:	Recommendations and Guidelines
Date Submitted by the Author:	n/a
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Defining trauma-induced coagulopathy with respect to future implications for patient management: Communication from the SSC of the ISTH

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Trauma-induced coagulopathy (TIC) is a clinical scenario spanning the spectrum of hypocoagulability to hypercoagulability causing a wide range of complications including uncontrolled bleeding and thrombotic disease. TIC is driven by tissue injury [1], where shock and hypoperfusion act synergistically to worsen and provoke TIC [2].

Defining the clinical syndrome of TIC has been hampered by the wide variations in patient presentation. Severely injured patients manifest diverse phenotypes of TIC spanning hypo- and hyper-coagulability and may rapidly progress between phenotypes. The presentation is chiefly thought to be a result of the variability of the magnitude and timing of the interaction between tissue injury and shock as well as resuscitation practices. Variations in experimental measurements such as timing of patient presentation, prior therapy, and timing to blood sampling complicate the definition of TIC [3–5].

As a result of the difficulty in defining clinical TIC, the underlying biochemical mechanisms of TIC are unclear. Factors contributing to a hypocoaguable state include impaired thrombin generation, impaired platelet function, deficient or defective fibrinogen, increased fibrinolysis, and endothelial dysfunction, while those contributing to hypercoagulability include excessive thrombin generation, endothelial injury, platelet hyperactivity and exhaustion, hyperfibrinogenemia, and impaired fibrinolysis [6–16].

In recent years, multiple definitions of the hemostatic disturbances in trauma have been published [17–20]. The unstandardized nomenclature and definitions (ATC; acute traumatic coagulopathy, TIC; trauma-induced coagulopathy, ACoTS; acute coagulopathy of trauma-shock, CoT; coagulopathy of trauma, DIC; disseminated intravascular coagulation, endotheliopathy of trauma and hemorrhagic blood failure [21], shock induced endotheliopathy (SHINE [5,6]) used to describe these derangements in trauma has led to a considerable degree of confusion within the field [22–25].

This communication, from the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) on fibrinolysis, DIC, and perioperative and critical care thrombosis and hemostasis, builds on a previous consideration [26] and provides (a) an overview of the current leading theories of the mechanism of TIC, (b) compare and contrasts the major overlapping lessons from coagulopathies related to other critical illnesses such as sepsis-induced coagulopathy, (c) addresses the critical knowledge gaps in our understanding of the pathophysiology of TIC, and (d) defines a new categorization scheme for patient groups to better stratify the likely coagulopathic phenotypes and pathophysiology based on the patients arrival characteristics. Together, addressing these knowledge gaps may provide a roadmap for the development of clinical and point-of-care diagnostic strategies for rapidly

and pre-emptively identifying the patient with TIC in order to optimize transfusion and resuscitation.

Current understanding of the mechanisms of trauma-induced coagulopathy (TIC)

The CRASH-2 trial demonstrated reduced mortality if tranexamic acid (TXA) is administered within 3 hours of the onset of trauma in patients at risk of bleeding, providing proof-of-concept for the acute management of coagulopathy in trauma [27]. The key coagulation system abnormalities have been attributed to (a) systemic endotheliopathy from tissue damage, ischemia, and resuscitation, and (b) the ensuing systemic inflammatory response to this injury, which is thought to trigger (c) platelet activation and dysfunction, (d) dysregulated coagulation factor activation including in thrombin generation and activated protein C, and (e) altered fibrinolysis through the release of tissue-type plasminogen activator (t-PA) and/or its inhibitor, plasminogen activator inhibitor-1 (PAI-1).

TIC is driven by two distinct and synergistic insults: hypovolemic shock due to blood loss and extensive tissue disruption (Figure 1) [28]. The variables that modify the TIC phenotype and course include (a) trauma: injury extent and severity, tissue type injured (head [29], orthopaedic [30]), degree of hemorrhagic shock, mechanism of injury (blunt,

penetrating/hemorrhagic [31,32]), and time from injury [3,7,20,33–36]; (b) patient factors: age, sex, medical comorbidities (cardiovascular disease), concomitant anticoagulant use, presence of other toxins including alcohol, heritable differences in baseline coagulation; and (c) resuscitation strategies: types of fluids used, the impact of blood components, adjuncts such as TXA, and timing of surgical intervention [20,33,36]. The combination of these three variables distinguishes TIC from the other acute coagulopathies (*i.e.* open cardiovascular surgery, liver transplantation, postpartum hemorrhage, sepsis, malignancy and autoimmune- and toxin-mediated coagulopathy) [37–39]. The timing, treatments, and complex interplay of variables lead to the various TIC phenotypes. Ongoing dysregulation of coagulation may eventually lead to a final common pathway of fulminant coagulation failure and the clinical presentation of disseminated intravascular coagulation.

Impaired clot formation is driven by both hypoxia and tissue injury (Figure 2) [28]. Proposed mechanisms include the activation of protein C with subsequent deactivation of factor (F) V and FVIII, and the release of heparan sulfate and syndecan-1 from the endothelial glycocalyx [6,40]. Systemic hyperfibrinolysis is stimulated by hypoxia with endothelial release of t-PA, and thrombin generated by activation of coagulation also stimulates t-PA release.

Fibrinolysis can be inhibited via the byproducts of tissue injury and activation of platelets releasing antifibrinolytic agents such as PAI-1 [28].

Coagulopathic patients can harbor hypofibrinogenemia early after injury, which can be a marker of TIC, and is dose-dependently related to shock, injury severity, and mortality [22]. Depletion is associated with poor outcomes, an effect which can be reversed with supplementation [41]. Low fibrinogen concentrations correlate with increased transfusions, ventilator days, and increased early and late mortality [42]. Fibrinogen supplementation improves clot initiation and stability [43,44], and may decrease mortality in this group [45]. A large observational study in combat-injured patients in Afghanistan suggested that supplementation with cryoprecipitate may have independent survival benefit [46]. Current European guidelines suggest the early empiric administration of higher concentrations of fibrinogen [47], although the benefits are currently being assessed in a number of clinical trials [48].

Acute severe injury and haemorrhagic shock cause a complex response of the innate immune and inflammatory systems that are tightly coupled with the coagulation system [49]. Damage associated molecular pattern proteins (DAMPs) released during tissue injury [50,51] and ischemia/reperfusion [52–54] elicit time-dependent changes in coagulation and fibrinolysis

that may have common pathways; namely, immediate thrombin generation, t-PA availability, and later suppression of fibrinolysis by PAI-1 [55,56]. The behaviour of DAMPs in TIC may have similar and related responses after sterile injury to pathogen-associated molecular proteins (PAMPs) following infection, a response thought to regulate the severity and progression in sepsis and sepsis-induced coagulopathy [57,58].

Comparisons and lessons learned from sepsis-induced coagulopathy (SIC)

As with other coagulopathies, sepsis-induced coagulopathy (SIC) fundamentally differs from TIC in its pathophysiology, particularly in the early stage of the diseases. Common pathways are activated in both SIC and TIC, and as the dysregulated inflammatory and coagulo-fibrinolytic responses progress, they may converge on a final pathway of disseminated intravascular coagulation (DIC) (Figure 3).

The systemic infections that most commonly trigger SIC are with *Staphylococcus aureus, Streptococcus pneumonia, Escherichia coli,* klebsiella species, and *Pseudomonas aeruginosa* [59–61]. The clinical presentation is that of DIC and is thought to originate from loss of localization of clotting factor activation starting in the microvasculature. Patients present with either thrombotic or bleeding phenotypes, and the SIC timeline is unclear as the triggering

event to coagulopathy is likely distributed over a long phase of infection. The infectious trigger causes upregulation of multiple inflammatory biomarkers, leading to widespread fibrin deposition and microvascular thrombosis. Fibrinolytic shutdown appears to be a common occurrence and similar to late trauma [62]. TXA is not recommended in these patients as their recovery is dependent on fibrinolysis to lyse systematic thrombi.

Recent refinement of the diagnosis of SIC has suggested a unique pathophysiologic mechanism for sepsis when compared to other coagulopathies. This is of importance since refining the diagnosis of SIC allows for early individual treatment based on clinical and laboratory presentation [37–39,63]. Recent clarification of the distinction between what has classically been called DIC and other forms of acquired coagulopathy in the early stages have been noted to advance treatment for those coagulopathies with individualized diagnostic and therapeutic options [64].

Proposed stratification of TIC clinical presentation for investigation

The clinical presentation of coagulopathy in TIC can shift between two ends of the hemostatic spectrum depending on the time course [8,9], injuries, and prior treatments, where one clinical phenotype may be more dominant. This heterogeneous presentation and treatment,

complicated by complex and dynamic underlying pathophysiology is the likely source the incomplete definitions in the clinical presentation and course of the patient with TIC. We propose a clinical stratification to severely injured patients in order to better study and define the underlying mechanisms of the clinical phenotypes of TIC.

Currently there is no broadly accepted standard laboratory method to identify and prognosticate TIC. In the setting of severe injury and shock, elevated INR has been the most robust predictor of mortality, length of ICU stay, and 30-day survival [22,65,66]. These patients with elevated INR were more than 4 times likely to die, a finding consistent between military and civilian trauma registries. TIC has also been found in patients without severe traumatic injuries, although coagulopathy is associated with high ISS. Patients with a base deficit ≤-6 may also be monitored for underlaying coagulopathy or occult shock [35]. Viscoelastic assays such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are emerging point-of-care tools for providing a global view of hemostasis [67]. The clinical cutoffs of these tests are still under investigation [68].

Primary vs. secondary

TIC is a primary endogenous coagulopathy that is at least partly caused by dysregulated innate immune inflammatory host responses to trauma and traumatic shock, leading to organ

dysfunction and a poor outcome [7]. Anemia, dilution, hypothermia, and acidosis exogenously induce secondary coagulopathy, which can modify primary coagulopathy [35].

Early vs. late

In civilian [12] and military [13] settings, uncontrolled hemorrhage is the leading cause of preventable death following traumatic injury. Civilian studies reveal that more than 95% of deaths from hemorrhage occur within the first 24 hours of the onset of trauma, with a median time of approximately 3 hours [12]. The first hours of resuscitation are critical and require prompt identification and management to control local and systemic hemostasis. Patients in the "late" phase may have ongoing coagulopathy requiring a biochemically driven resuscitation strategy following surgical hemostasis.

Enhanced vs. inhibited fibrinolysis

In primary coagulopathy, trauma and traumatic shock give rise to systemic and persistent thrombin generation [7,14,18,24,50,56,69] associated with platelet dysfunction [15,16] from the early to late phases of trauma. Fibrinolytic systems bring about dynamic two-phases changes: increased fibrinolysis due to shock-induced t-PA release at an early stage

[50,70], and the inhibition of fibrinolysis due to persistent expression of PAI-1 at a later stage of trauma [51,71,72]. These imbalances are predictors of mortality in observational studies, and importantly, those patients with physiologic levels of fibrinolysis on admission have been shown to have the lowest mortality [8–11]. Although depending on the mechanism of injury, the type and speed of resuscitative measures imparted, the evolution from hyperfibrinolytic-type to hypofibrinolytic-type can occur in minutes to hours [10]. Increased fibrinolysis accelerates bleeding, thus leading to uncontrolled haemorrhage.

Resuscitation responders versus non-responders

Hemostatic changes in trauma are also modified by resuscitation leading to ischemia-reperfusion events, which can further derange coagulation. Early TIC is influenced by the degree of resuscitation which is a necessity in most cases. Also, therapeutic measures including surgical interventions and hemostatic resuscitation as a part of damage control resuscitation post injury can modify the late coagulopathy. Sustained systemic inflammatory response syndrome associated with the activation of tissue factor-dependent coagulation pathways and inhibition of fibrinolysis contributes to organ dysfunction in the late phase of trauma [9,10,51,73]. However, when resuscitative measures and the availability/accessibility of

allogeneic blood products may be limited (*e.g.* less-resourced nations or remote locations), the TIC spectrum may present a completely different picture, which often leads to early mortality.

Addressing knowledge gaps in the future

Identifying the molecular mechanisms that drive TIC, including the location of where coagulation occurs (*i.e.* intra- versus extra-vascular space segregated by the endothelial layer) is crucial for understanding the consequent pathophysiology of coagulopathy [24,26]. In addition, this segregation by the endothelial barrier inherently provides control of both anticoagulant (*e.g.* antithrombin and negatively charged glycocalyx, activated protein C) and fibrinolytic (*e.g.* PAI-1, α_2-antiplasmin) phenotype. Understanding of the haemostatic effects of the damaged/activated endothelium in TIC that consequently leads to pathologic coagulopathy is needed to better understand TIC and improve its treatment strategies.

In addition, an agreed upon definition of TIC will subsequently allow for clarification and identification of the knowledge gaps that exist. These gaps include identifying: 1) factors that regulate progression of TIC to DIC, 2) the differences between primary pathogenic mechanisms driving SIC versus TIC, 3) the significance of dysregulated fibrinolysis and

anticoagulation in TIC, 4) the distinguishing characteristics of early and late phenotypes in TIC, 5) the role of platelet dysfunction in SIC and TIC, and 6) the diagnostic criteria of SIC and TIC.

Summary

TIC is a clinical disease process that encapsulates multiple defects to major systems in hemostasis in the acutely severely injured patient. Patients at various stages can present on a spectrum between bleeding and thromboembolism, with untreated TIC leading eventually to a picture of fulminant DIC. Heterogeneity in patient injury factors complicate the definition of the clinical presentation of TIC, study of the underlying pathophysiology of TIC, and devising optimal strategies for treating the primary defects in TIC. To decrease the heterogeneity, this communication proposes that the study of trauma patients suffering from TIC be assessed on the following factors: i) primary or secondary coagulopathy based on the pathophysiology, ii) early or late coagulopathy based on the timing, iii) increased or inhibited fibrinolysis phenotypes based on the dynamics of fibrinolysis, and iv) resuscitated or non-resuscitated state based on the rescue measures provided. If adopted, these steps could dramatically improve patient care in the acute stages of trauma and facilitate examination of the underlying pathophysiological mechanisms.

Conflicts of Interests

SG is a consultant for Asahikasei Pharma America and has received honorarium from Asahikasei Pharma Japan. EEM is a co-founder of ThromboTherapeutics, holds equity in Haemonetics, and has received research funding from Haemonetics, Instrumentation Laboratory, and Stago. MDN holds equity as a board member at Haima Therapeutics, received honoraria from CSL Behring and Janssen Pharmaceuticals, received research funding from Haemonetics, Instrumentation Laboraties, Noveome, and Accriva Diagnostics. HBM is a co-founder of ThromboTherapuetics and receives research support from Instrument Laboratories. ES has received honoraria from Danube University of Krems, Weill-Cornell Medicine, University Hospital Zurich Foundation, CSL Behring, and EurAsia Heart Foundation. MAS is a consultant for Haemonetics, Arsenal Medical, and Velico Medical. JHL is on the advisory board for CSL Behring, Instrumentation Laboratories, Janssen, Octapharma, Leading Biosciences, and Merck. MW holds research grants from Haemonetics and has received honoraria from Portola Inc. All other authors have no conflict of interest to report.

Author Contribution

HBM, SG, TI, PYK, CHY, MDN, RLM, EEM, NJM, and MW wrote the manuscript and participated in the consensus discussion. EEM, HBM, SG, and TI generated the figures and PYK edited the figures. KB, BJH, JHL, DFD, SS, KG, MAS, CDB, JT, TU, ST, and ES contributed by participating in the consensus discussion and editing of the manuscript.

Figure Legends

Figure 1. Mechanisms of impaired clot formation in TIC. Impaired clot formation is driven by both hypoxia and tissue injury. Proposed mechanisms include the generation of activated protein C with subsequent deactivation of factors Va and VIIIa, and the release of heparan sulfate from the endothelial glycocalyx. Adapted from Moore *et al.* [28]

Figure 2. Factors regulating fibrinolysis in TIC. Systemic hyperfibrinolysis is stimulated by hypoxia with endothelial release of t-PA that activates plasminogen. On the other hand, fibrinolysis is inhibited via the by-products of tissue injury and activation of platelets releasing antifibrinolytic agents. Adapted from Moore *et al.* [28]

Figure 3. The overlap of SIC and TIC. Adapted from Iba *et al*. [37]

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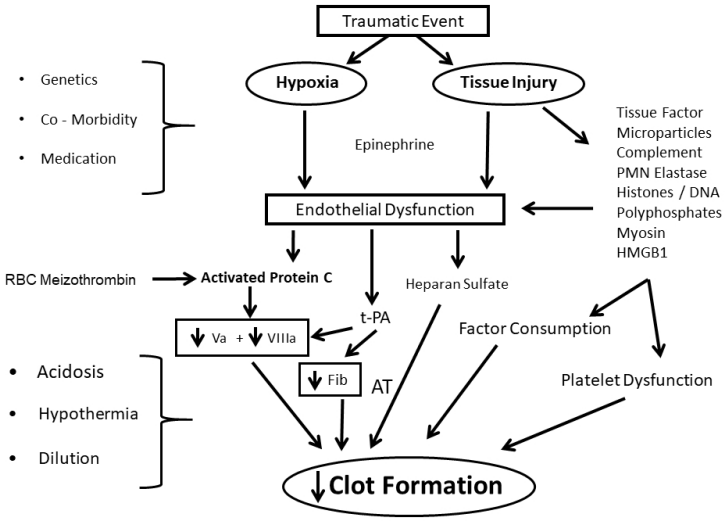

Figure 1

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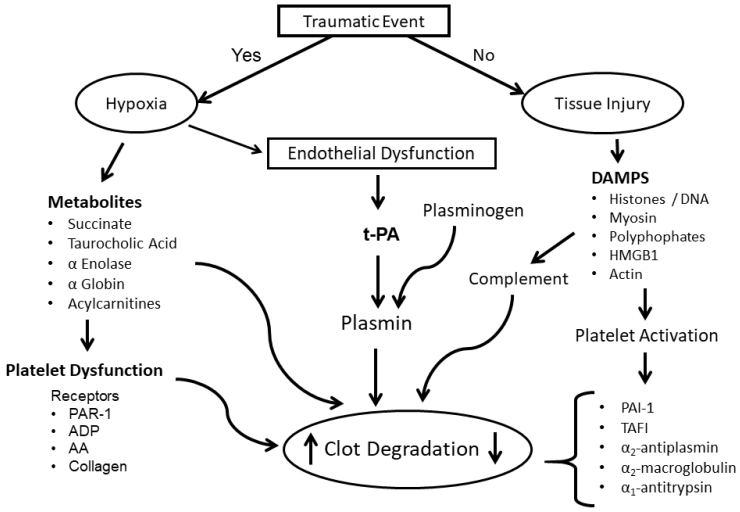

Figure 2

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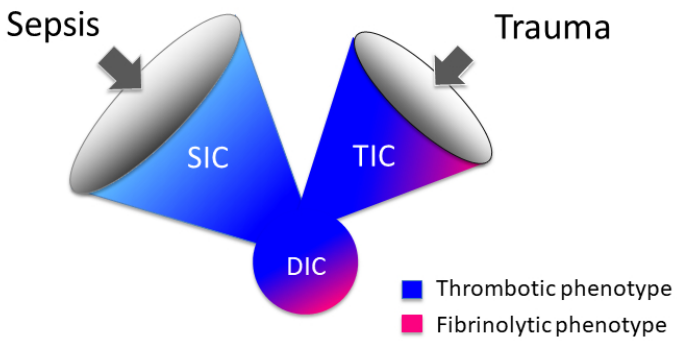

Figure 3

254x190mm (96 x 96 DPI)