TRAUMA INDUCED COAGULOPATHY

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Abstract

Uncontrolled hemorrhage is a major preventable cause of death in trauma, the latter accounting for 9% of global deaths. There is no agreed definition of trauma-induced coagulopathy (TIC), the term is used to describe abnormal coagulation attributable to trauma. Early TIC occurs within 6 hours of injury and is characterized by hypocoagulability resulting in bleeding; whereas late TIC represents a hypercoagulable state associated with thromboembolic events and multiple organ failure.

Research into pathophysiological mechanisms have recognized that acute blood loss, metabolic acidosis, endothelial activation, immune system of activation, platelet activation, and traumatic brain injury account for the diverse phenotypes of TIC. Multiple haemostatic abnormalities have been described including fibrinogen depletion, inadequate thrombin generation, platelet dysfunction, dysregulated fibrinolysis, and endothelial dysfunction resulting in various phenotypes. Diagnosis is made by detecting abnormalities in viscoelastic haemostatic assays (VHA) or coagulation screening especially prolonged prothrombin times.

Management priorities are controlling blood loss and reversing shock with balanced ratios of blood products; alongside prehospital tranexamic acid in long transport or austere environments. There is no international agreement on the composition of initial blood components for presumed TIC. For those who survive, there are high rates of morbidity especially in those with traumatic brain injury, which dominates short and long term quality of life and functional outcome.

[H1] Introduction

Injury is the fourth leading cause of mortality worldwide, accounting for 9% of world's deaths and claiming 4.9 million lives worldwide in 2016[1]. Moreover, the burden is higher in individuals younger than 50 years, among whom injury as a cause of death is second only to infectious diseases. Early **preventable deaths** (Box 1) after injury in civilian [2] and military [3] settings are primarily attributable to uncontrolled hemorrhage[2-8] while later **preventable deaths** are attributed to hypercoagulability[9]. Consequently, there is intense interest worldwide in the pathogenesis of trauma-induced coagulopathy (TIC) to attenuate its adverse effects on outcome of the seriously injured patient.

Impaired coagulation following sudden death from injury has been appreciated for centuries[10]. In the 1960's the first clinical laboratory documentation of the temporal changes in coagulation following severe injury were documented[11]. However, specific interventions to address these early endogenous changes in coagulation were not specifically addressed until 1982 when a case series of major abdominal vascular injuries highlighted trauma-induced coagulopathy (TIC) as a common direct cause of early postinjury mortality, observing that 89% of the deaths were bleeding-related, yet half occurred after mechanical control of bleeding sites, i.e., due to coagulopathy[12]. Management of these physiologic derangements include **damage control resuscitation** (early blood products, avoiding hemodilution with crystalloids, and hypotensive resuscitation)[13,14] and **damage control surgery** (temporary packing of bleeding sites until reversal of TIC)[15,16] (Box 1). However, the remaining ongoing quagmire is the inability to distinguish between patients with exsanguinating injuries whose TIC is provoked by metabolic failure ("bleeding because they are dying"), from patients whose TIC is the cause of ongoing blood loss ("dying because they are bleeding")[17]. Furthermore, not all patients with abnormalities in laboratory coagulation tests are bleeding [18].

Despite the long-term fascination with changes in coagulation resulting from shock and tissue injury[19191919191818181919], there is no standard definition of TIC. TIC refers to abnormal coagulation capacity attributable to trauma. TIC can manifest in a spectrum from hypo- to hyper-coagulation (**Figure 1**), as a function of several interactive factors, including (but not limited to): tissue injury, presence of shock and, especially, time from injury (**Figure 2**). For discussion purposes, we suggest the terms early and late TIC, but acknowledge that the phenotypes can vary substantially within these time periods. Early TIC (generally within 6 hours of injury) is characterized by the inability to achieve hemostasis, which may lead to uncontrolled hemorrhage and protracted shock; whereas late TIC (usually >24 hours postinjury) is represented by a hypercoagulable state, which may result in excessive macro- and micro-clotting leading to thromboembolic events (e.g., deep venous

thrombosis and pulmonary embolism) or to acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). Early and late TIC are not mutually exclusive, i.e., patients may develop early TIC due to massive blood loss but succumb to extensive microvascular occlusion recognized as irreversible shock. Furthermore, the transition from hypocoagulability to hypercoagulability may occur within minutes / hours or delayed for days**.** The National Institutes of Health (NIH) conducted a Trans-Agency Coagulopathy in Trauma Workshop in April 2010. Out of this meeting came the consensus for the term “trauma-induced coagulopathy” (TIC) to describe these phenomena.

Despite the lack of a clear definition of TIC, there appears to be agreement on a related but distinct syndrome, disseminated intravascular coagulation (DIC). DIC is defined as "an acquired syndrome characterized by the intravascular activation of coagulation with a loss of localization arising from different causes"[20]. Recently, a consensus statement from the International Society of Thrombosis and Hemostasis (ISTH) clarified the common as well as distinct mechanisms of DIC versus TIC[21]. Early TIC is dominated by acute blood loss with associated shock (ischemia/reperfusion), impaired clot formation and, in advanced cases, hyperfibrinolysis (**Figure 1**). Following trauma, tissue factor (TF) facilitates clot formation at sites of endothelial injury; whereas, in DIC there is unbridled systemic clotting promoted by TF expression on a number of cell surfaces. Ultimately, late systemic prothrombotic/antifibrinolytic TIC mirrors certain DIC phenotypes[22].

In this Primer, we will describe what is known of TIC, but perhaps more importantly will acknowledge what remains to be defined (**Box 2**). Our primary objective is to provide a broad picture of the entity TIC to inspire investigators from diverse disciplines to pursue answers to the substantial gaps in knowledge.

[H1] Epidemiology

Uncontrolled bleeding causes 25% of all injury-related deaths [23-31], and 40-80 % of **potentially preventable deaths** [32], (**Box 1**) both in military and in civilian settings (**Table S1**). At least a quarter of these are likely to have a TIC component[33]. The phenomenon is observed globally: Australian[29] and Canadian[34] studies implicated hemorrhage in 15-33% of injury deaths. In Stavanger, Norway, 25% of the 1996-2004 trauma deaths were due to exsanguination.[30] In a Turkish hospital, from 2010-2013, circulatory collapse accounted for 33% of injury mortality.[35] In Brazil, hemorrhage claimed 18% of the trauma deaths in an urban hospital.[36] Although two European studies[37,38] exhibited lower proportions of hemorrhagic deaths, these studies classified polytrauma, chest injury, and cardiac arrest as separate, non-hemorrhagic causes of death. Differences in populations, injury mechanisms as well as healthcare resources explain the disparities in statistics. Since the 1990’s when bleeding caused over one third of trauma fatalities[24,], we have made little progress as hemorrhage accounts for 20-34% of current trauma mortality.[28,39] While a US urban trauma center observed a reduction in bleeding deaths after implementing a **bleeding-control bundle-of-care** (from 36% to 25%)[31], (Box 1) hemorrhage remained frequent among potentially preventable deaths (48% vs. 43%)[40].

Understanding the timing of hemorrhagic deaths is crucial to determine when hemostatic therapies are most effective, and which outcomes (i.e., massive transfusion, all-cause vs hemorrhagic deaths, early vs late mortality) they may affect [4,41]. Trauma deaths immediately postinjury are often due to irreparable injuries, thus hemostatic interventions are likely to impact hemorrhagic deaths over the ensuing hours. Randomized controlled trials (RCT)[2,5,6,14,42-44] and observational studies[34,35,45] unequivocally show that hemorrhagic deaths occur within 24 hours, mostly within 3-6 hours. TBI competes as a dominant cause of death in the 6-24-hour period and multiple organ failure (MOF) predominates after the first week[2]. In the CRASH-2 trial, representing primarily developing countries, 34% of all deaths were attributed to bleeding, 50% within 10 hours.[43] Analyses of three recent US randomized controlled trials focusing on postinjury hemorrhage control, with relatively similar populations, methods, and healthcare resources, most hemorrhagic deaths occurred in the first 6 hours (**Figure 3**). [7,46] Half of all deaths in the first 3-6 hours in these three RCTs were due to hemorrhage.

The incidence of TIC diagnosed via laboratory tests varies widely (**Table S2**) but most studies converged around a TIC incidence of 25% of severely injured patients, with an associated 35-50% mortality. Tissue injury severity and shock/ hypoperfusion are the major risk factors (**Table S2**). Civilian[47] and military[48] studies indicate that TIC is accentuated when

both exist. Metabolic acidosis and penetrating mechanism are commonly reported TIC risk factors (**Table S2**). Very young children develop TIC more frequently than older children, and children in general develop TIC later and less frequently than adults[49]. The elderly are more vulnerable to TIC than younger adults[50,51]. Longer prehospital times[52] and prehospital crystalloids[52,53] worsen TIC. TIC's magnitude correlates with traumatic brain injury (TBI)'s severity (Table S2), but studies[54,55] suggest that hypoperfusion is an important cofactor. An often-neglected factor is hypocalcemia, caused both by shock and citrated blood products (especially plasma and platelets), and it has been suggested that the "lethal triad" should include hypocalcemia and become the "lethal diamond"[56,57]. On the other hand, it is important to recognize that while TIC is common in the severely injured, many patients with laboratory-based TIC do not have substantial bleeding[18].

[H1] Mechanisms/pathophysiology

[H2] Hemorrhagic Shock

The pathophysiology of hemorrhagic shock is fundamentally blood volume depletion with diminished oxygen delivery to the microcirculation, ultimately resulting in metabolic acidosis. Although isolated transient hemorrhagic shock may be tolerated, compounded by tissue injury, hemodilution, and acidosis it is a major driver of TIC. It is important to distinguish early, hypocoagulable TIC (**Figure 2**) from iatrogenic coagulopathy due to resuscitation with large volumes of cold fluids and blood products, which leads to: 1) dilution of enzymes required for clot formation, and 2) hypothermia, which impairs clotting factor activity and platelet function[12,58]. The hypocoagulable TIC phenotype can be attributed partially to metabolic acidosis due to reduced blood perfusion of tissue beds and organs[52,59-63]. In animal studies and in vitro experiments, acidosis has been shown to retard polymerization and clot strengthening in **viscoelastic tests**[60], (**Box 1**) decrease factors V and IX activity and platelet aggregation[64], increase fibrinogen consumption[61], reduce platelet count, thrombin generation, and maximum clot strength, and induce abnormal conventional coagulation tests[59]. A pH drop from 7.4 to 7.2 reduces the activity of each of the coagulation proteases by more than half [63,65]. A swine model showed that acidemia (pH 7.1) was associated with depleted plasma fibrinogen by 34%, platelet count by 51%, and thrombin generation in the propagation phase by nearly 50%. Hypothermia is now less frequent with modern hemostatic, **goal-directed resuscitation** (**Box 1**) with warm fluids [66,67], but it should not be overlooked. Wolberg and colleagues [68] in an in-vitro study of healthy volunteer blood, noted a significant reduction in both platelet function and coagulation enzyme activity at temperatures <33 °C. Hypothermia remains a marker for poor prognosis after hemorrhage, probably representing metabolic dysfunction[52,69-71] Shock also leads to **auto-dilution**, (**Box 1**) i.e., shifts of interstitial fluid into the vascular compartment, which may impair hemostatic capacity[72].

Activation of protein C (aPC) may be a contributing mechanism [33,54,55,73]. Trauma-induced hypoperfusion has been reported to activate PC, which may inactivate factors V and VIII, and is associated with reduced plasminogen activator inhibitor-1 (PAI-1). Elevated aPC predicts adverse postinjury outcomes, however, the mechanistic role of aPC in TIC has been disputed. Specifically, platelets and plasma Factor Va are resistant to aPC cleavage at concentrations of aPC seen in TIC[72]. While hypothesized that aPC binds to PAI-1 and thus de-represses t-PA, it seems more likely that the enormous release of t-PA from endothelium is due to epinephrine, vasopressin, and thrombin signaling as well as hypoperfusion, which drives the fibrinolytic phenotype of TIC[74].

In addition, metabolic byproducts, such as succinate, have been associated with early TIC[75], and oxidative stress has been shown to modify fibrinogen polymerization resulting in weaker clots[76]. Finally, hypocalcemia is another mechanism by which hemorrhagic shock can impair coagulation. Calcium plays an important role in the formation and stabilization of fibrin polymerization sites and, consequently, it has an impact on all platelet-dependent functions[77]. Yet laboratory coagulation tests may mask the negative impact of hypocalcemia on coagulation, as blood samples are re-calcified prior to being assayed. Hypocalcemia is prevalent post-hemorrhage [53], due to resuscitation with citrated blood products, and low

hepatic clearance of citrate due to defective hepatic perfusion[78], as well as other still poorly understood shock-related mechanisms[56,67].

With the progression of the shock state, hypercoagulability ensues due to prothrombotic changes and fibrinolysis shutdown promoting organ damage by generating thrombi and occluding the microvascular circulation, leading ultimately to organ failure[9,79]. Hypocoagulability and increased fibrinolysis during shock may well represent intrinsic mechanisms to prevent these events from occurring; it remains debatable whether these are adaptive or pathologic responses[80].

[H2] Tissue Injury

Tissue damage with endothelial disruption activate the coagulation system at the injury site via expression of TF, a transmembrane protein expressed within the subendothelium that becomes exposed. TF complexes to FVIIa and activates the coagulation system resulting in thrombin generation and fibrin formation[81]. Moreover, tissue trauma provokes the release of damage associated molecular patterns (DAMPs), which stimulate inflammatory pathways by the release of a number of mediators. Haemostasis and inflammation are interrelated processes that robustly influence one another.

TIC's development is typically associated with the severity and extent of tissue injury[48,82-84]. Tissue damage and shock-related hypoperfusion occur together frequently; however, their synergistic contribution to TIC remains unclear. Multiple potential pathways have been suggested, including an early effect of DAMPs on platelet function, rendering them hyporesponsive[80,85]. Furthermore, an initial thrombin surge would activate endogenous anticoagulation pathways, and some component of clotting factor consumption may occur in TIC, distinct in mechanism from DIC[21]. It is also possible that the pattern of tissue damage contributes to TIC. For example, TBI creates a hypocoagulable state as the cerebral tissue contains potent procoagulant molecules such as phospholipids, which deplete clotting factors, and provoke platelet inhibitors[86]. Damage of organs with high content of tissue plasminogen factor (tPA), such as the pancreas, lung and urogenital system, may also compromise haemostasis via fibrinolytic activation. However, the exact contribution of these organ injuries are unknown. It is similarly unclear whether any pre-existing chronic conditions in those tPA-rich organs may modulate TIC dynamics. Adding complexity, tissue injury has also been directly correlated with fibrinolysis shutdown through release of cellular by-products of injury, as well as mechanical trauma to red blood cells and platelets releasing their contents[87]. A recent study suggested that myosin can bind factors Xa and Va, consistent with their ability to create prothrombinase that promotes thrombin activation[88]. Tissue injury has been shown in both pre-clinical models and patient studies to result in the production of extracellular vesicles from multiple cellular sources, which are strongly prothrombotic and may result in coagulation factor depletion after injury [89,90].

[H2] Endothelial Dysfunction

The endothelial cell surface network governs coagulation, inflammation, micro-circulation, and barrier function critical to vascular homeostasis and oxygen delivery (**Figure 4**). TIC's damage to this network, termed the endotheliopathy of trauma (EOT), is characterized by loss of barrier function, leukocyte adhesion, endothelial activation, and clinical expression of coagulopathy, micro- and macro-thrombosis, and organ dysfunction, and is likely mechanistically circular, in which TIC contributes to EOT and vice-versa[91]. The role of the contact activation system as a result of collagen exposure remains unclear[92]. The contact activation system includes the plasma proteins FXII, prekallikrein, and high molecular weight kininogen (HK). FXIIa cleavage of prekallikrein results in the serine protease kallikrein, which can cleave HK to generate bradykinin. Bradykinin can induce both the expression of tissue factor (procoagulant) as well tPA (profibrinolytic).

EOT is mediated by hypoperfusion and is characterized by circulating markers of shed endothelial glycocalyx associated with coagulopathy, inflammatory complications, vascular thrombosis, organ failure, and death (**Figure 4**)[93-95]. The glycosaminoglycan syndecan-1 is the most well-characterized sheddase in TIC[91], as its heparan sulfate domain is shed with hemorrhage and hypoperfusion, catecholamine surges, and oxidative stress. It remains controversial whether auto-heparinization from the heparan sulfate domain contributes to impaired clot formation, as it is variably identifiable by viscoelastic assays[96]. Pathologic cleavage of the syndecan-1 ectodomain may be mediated by MMPs of the A Disintegrin and Metalloproteinase (ADAM) family. However, whether poor outcomes associated with shed proteoglycans are direct or downstream to altered protective glycoproteins is unclear. Experimental work suggests that tissue injury- and the shock-

driven thrombin-thrombomodulin system activation, and ultimate depletion of protein C, diminish endogenous cytoprotective effects to the endothelium[54,73,97]. Additionally, altered platelet-endothelial regulation in TIC may disrupt an important symbiosis, as soluble CD40, a primarily platelet-derived ligand of endothelial inflammatory cascades, is associated with TIC[98]. Further, both sustained exocytosis of structurally ultra-large von-Willebrand factor (vWF) and impaired MMP ADAMTS13 clearance of vWF are identified in injured patients with TIC [99], and are associated with prothrombotic and proinflammatory biology[99,100], highlighting the importance of endothelial biology in mediation of micro- and macro-thrombosis (**Figure 4**).

Animal studies show that endothelial barrier function is restored with plasma [91,101-104], and early plasma of injured patients is associated with reduced circulating syndecan-1[105], providing mechanistic insights for improved outcomes [5,6]. ADAM MMP cleavage of syndecan-1 ectodomains may be mitigated with plasma treatment via Tissue Inhibitor of Metalloproteinase (TIMP) inhibition or decreased activation of ADAM MMPs. Additionally, newer hypotheses around mechanisms of tranexamic acid in injured patients center on abrogation of the EOT through serine protease inhibition, DAMP mitochondrial DNA release suppression, mitochondrial respiration stimulation, and oxidative phosphorylation enhancement[106,107]. It remains unknown whether the EOT is cause or effect in TIC, but identification of therapeutic targets for recovery of endothelial cell surface networks, including characterization of soluble reparative molecules in plasma, continues to be investigated.

[H2] Cell-based Model of Hemostasis

The key concept underlying "cell-mediated hemostasis" is that cells play active roles in regulating and localizing the coagulation reactions [108]. Receptors, lipids and other features of cell surfaces are critical to defining the roles of specific cell types in hemostasis. Many cells participate in hemostasis, but platelets and endothelial cells are the two critical players. Platelets adhere at a site of injury and provide the surface on which procoagulant reactions occur, as well as controlling the rate and localization of thrombin production. Normally endothelial cells are actively antithrombotic, thus preventing propagation of clotting from a site of injury throughout the vasculature. A failure of cell-mediated regulation can lead to failures of normal hemostasis, even when the protein components are within normal ranges. This concept is particularly relevant to understanding the mechanisms of bleeding and thrombosis induced by trauma.

In the cell-based model, the process of hemostasis consists of the overlapping events of initiation (extrinsic pathway on TF-bearing cells), amplification (positive feedback of thrombin on platelets) and propagation of large-scale thrombin generation (intrinsic pathway on activated platelets) that are regulated by cell surfaces rather than the protein components alone (**Figure 5**).

The biochemical reactions of physiologic hemostasis are subject to several control levels. Some are reflected in the "coagulation cascade" that is focused on the roles of the various procoagulant factors (**Figure 6**). However, additional regulation levels involve the anticoagulants and protease inhibitors, as well as the cellular and tissue localization of coagulation. These control mechanisms are barriers to the activation and spread of coagulation, and thereby prevent clot formation at inappropriate times and places. Physiologic coagulation (hemostasis) is terminated when the area of injury is surrounded by a platelet/fibrin clot that stops bleeding, forms a physical barrier to the diffusion of activated factors and a provisional scaffold for healing to occur.

Coagulopathy occurs not only when procoagulants are consumed or diluted, but also when one or more of the control mechanisms is disrupted. Thus, not only the amount of thrombin generation can be abnormal, but its localization can be abnormal as well. Because trauma is such a heterogeneous event, it is difficult to define a dominant mechanism of coagulopathy in trauma. Furthermore, hemostatic function changes over time as bleeding continues, compensatory mechanisms are engaged and inflammation progresses.

[H2] Platelet Dysfunction

Despite being subcellular in size and anucleate in structure, platelets are biologically dynamic in coordination of hemostasis, endothelial health, and immune function[109-111]. Interest in the platelet role in TIC intensified following the description of the above-mentioned cell-based model of hemostasis in 2001[108]. Subsequent accumulating evidence has supported the presence of quantitative and qualitative[112] deficits in primary hemostatic and secondary endothelial and immune-regulatory platelet functions[113,114], in human and animal TIC models, and implicated platelets in the pathogenesis of postinjury venous thromboembolism (VTE) and multiple organ failure (MOF).

Platelets are central in structure and function to primary procoagulant protein assembly, thrombin generation, fibrin crosslinking, and fibrinolytic regulation, and secondary endothelial and immune regulation (**Figure 4**). Failures of both primary and secondary platelet functions are characteristic of TIC, and can be identified in up to 50% of injured patients, regardless of severity of injury or presence of shock[112]. Quantitative consumptive and dilutional thrombocytopenia are independently associated with bleeding[115,116]. However, most patients with TIC have preserved platelet counts, evidence of circulating populations of activated platelets, yet paradoxically impaired *ex-vivo* aggregation responses[117,118]. Phenomenologically, some describe this as "platelet exhaustion", due to injury and shock[119] driven by endothelial release of TF, platelet activating factor, and vWF[100,120], activating platelets beyond what is needed for primary hemostasis at the local sites of injury, creating circulating platelets that are expended following release of their pro and anticoagulant factors. It is hypothesized that these circulating expended platelets cannot contribute to primary hemostasis, nor *ex vivo* aggregation assays that require platelets to respond to stimulation[112,119]. Injured patients with impaired platelet aggregation responses also exhibit increased sensitivity to tPA mediated fibrinolysis, perhaps due to impaired platelet PAI-1 release[121]. Importantly, these acquired platelet dysfunctions of TIC may not be reversed by room temperature platelet transfusions[122,123], which may be due to injury and shock induced circulating platelet inhibitors[124]. Cold-stored platelets may be more effective in restoring platelet contribution to hemostasis.[125,126]

Efforts for deeper molecular phenotyping[90,127-130] have uncovered multiple molecular phenotypes of platelet dysfunction characteristic of TIC, both adaptive and maladaptive in nature (**Figure 4**). Beyond the primary effects of platelets contributing to early TIC and hemorrhage, TIC associated immuneregulation of platelets likely contributes to later TIC hypercoagulability [114,131]. Specifically, injury induced platelet activation stimulates platelet and leukocyte ligand binding inducing circulating platelet-leukocyte aggregates (PLA), associated with production of procoagulant milieus through the release of platelet factor-4, and increased expression of TF, fibrinogen, and factor Xa in animal models. Further, platelet-mediated toll like receptor-4 (TLR-4) signaling, histone H4 decoration of platelet procoagulant ballooning, and platelet-derived high mobility group box-1 (HMGB-1) recruitment of monocytes and neutrophil extracellular trap formation[90,132,133] are all proinflammatory mechanisms identified in association with early failures in platelet hemostasis and later hypercoagulability.

Whether the diverse qualitative changes in platelet behavior characteristic of TIC are amicus or adversary remains unclear[80], begging for platelet biomarker, microfluidics, cell-culture, mitochondrial, ultra-structure microscopy, and genomic methods to uncover platelet targets for alternative TIC therapies beyond human-donated blood products[90,100,127,134,135].

[H2] Inappropriate Thrombin Generation

In initial phases of bleeding, thrombin generation (TG) appears to be insufficient, while later it may contribute to adverse thrombotic events. The final thrombin concentration is essential for the structure of the developing fibrin clot. Impaired thrombin concentration results in clots composed of thick fibrin fibres with diminished stability, which are prone to fibrinolysis. Thus, the balance between TG and inhibition is critical to hemostatic capacity. Depletion of endogenous inhibitors after injury can offset a decrease in procoagulants and increase risk for thromboembolic complications. [136,137]

TG can be altered by dilution of coagulation factors following fluid therapy, rapid coagulation factor consumption immediately post-injury, shock related systemic acidosis and hypothermia.[65,138-140] Severely injured patients are prone to an

early reduced Factor V [5,141,142] and Factor VII levels [142], and low Factor X[142] and fibrinogen concentration [140,142]. However, the reports of decrease in the activity of coagulation factors following severe injury are inconsistent. Concentration of coagulation factors >30% of normal are generally accepted as sufficient for effective hemostasis[143], although this threshold is based on work with single factor depletion. Data from the prehospital COMBAT study revealed that coagulation factors activity in severely wounded patients were all over 64% upon hospital arrival.[5]

Importantly, a reduction in procoagulants is not necessarily accompanied by impaired TG[142,144]. Even though multiple procoagulants were found to be lower in trauma patients, TG circulating markers (including prothrombin fragment$_{1-2}$ and thrombin-antithrombin complexes) were higher compared to uninjured subjects or patients without evidence of TIC[142]. Elevation of these markers reflects formation of thrombi in needing sites and may constitute a physiologic response to injury, with increased TG *in vivo* leading to both pro-and anti-coagulant depletion[201]. Importantly, standard coagulation assays do not reflect the activity of the anticoagulant systems. Thus, a slightly prolonged assay could reflect a modest depletion of procoagulants, which is not necessarily accompanied by diminished TG and a bleeding tendency *in vivo*, given that it is offset by depletion of anticoagulants [144,145]. Blood samples from trauma patients displayed a higher peak "native" plasma (no activator added) thrombin concentration than healthy individuals despite prolonged standard coagulation tests[144]. Recent data indicated that upon hospital admission, trauma patients exhibited 2.5-fold higher average plasma TG compared to uninjured subjects[146]. However, low TG capacity was evident in 17% of those patients. Notably, a peak TG <250nM was linked to 4-fold increased odds for massive transfusion requirement, and 3-fold greater odds of 30-day mortality[146]. Furthermore, there may be significant differences between plasma and whole blood thrombin assays [200.] Recent data with whole blood TG data indicate patients who required a massive transfusion had TG below normal controls [20] With respect to late TIC, thrombin is at the cross-road of coagulation and inflammation (**Figure 7**), and excessive thrombin generation may have an important role in delayed hypercoagulability in the injured patient. [137]

[H2] Fibrinogen Depletion

Fibrinogen is the most abundant coagulation factor in blood, with circulating levels in the range of 2-4g/L in a healthy adult, and a circulating half-life of approximately 4 days. Conversion of fibrinogen to fibrin occurs via thrombin-mediated cleavage at two sites (**Figure 8**), exposing binding sites for other fibrin molecules, thereby giving rise to spontaneous polymerization. Each fibrin fiber is comprised of several hundred to several thousand protofibrils aligned side by side, therefore providing extraordinary strength and resilience to the scaffold protein[77]. Fibrin fibers are cross-linked by the transglutaminase enzyme, activated factor XIII, providing additional mechanical strength and resilience to the fibrinolytic degradation[147]. In addition, fibrinogen binds with high affinity to integrin αIIbβ3 (also termed glycoprotein IIb/IIIa) on platelets, thereby facilitating further platelet aggregation, and generating force to contract the fibrin matrix and stabilize the forming clot.

Fibrinogen is synthesised by hepatocytes, with approximately 98% of circulating human fibrinogen being derived from the liver[148]. Circulating fibrinogen levels increase up to 20-fold in the acute phase response, mediated by IL-6 release following tissue injury, infection and inflammation[149]. Intriguingly, despite its high circulating concentration, fibrinogen is the first coagulation factor to reach critically low levels in severe bleeding events[150,151]. In major trauma, key contributors to hypofibrinogenemia include hemodilution (due to fluid resuscitation), blood loss, consumption in clot formation at the wound sites, hypothermia (which impairs fibrinogen synthesis), fibrinogenolysis and increased degradation due to acidosis[139,151]. Trauma and hemorrhagic shock are associated with a hyperfibrinolytic state, occurring in the first few minutes and sometimes persisting for hours following injury[152]. These observations are linked to excessive release of tPA from the endothelium, which swamps availability of its natural inhibitor PAI-1[153], thereby driving activation of circulating plasminogen to plasmin. Increased plasmin generation shifts the balance of the fibrinolytic system, promoting premature breakdown of fibrin in clots, and also fibrinogen degradation.

Low fibrinogen levels upon admission are independently associated with an increase in injury severity and shock[154]. Moreover, the fibrinogen level upon admission is an independent predictor of transfusion, 24-hour and 28-day mortality[154-156]. Fibrinogen level has been identified as the most important independent predictor of mortality, but whether this value

represents a biomarker (as opposed to mediator) in trauma patients remains to be determined. Current guidelines recommend fibrinogen supplementation in patients with traumatic bleeding when fibrinogen concentration is <1.5g/L[157].

[H2] Dysregulated Fibrinolysis

Fibrinolysis activation following severe injury has been documented for over half a century[11]. While the exact pathophysiology remains unclear, hemorrhagic shock is common in patients who present to the hospital with elevated fibrinolytic activity [9,158-161]. Hyperfibrinolysis is associated with elevated levels of tPA[153,162]. The source of tPA release during hemorrhagic shock is presumed to be Weibel-Palade vesicles in the endothelium released in response to multiple stimuli[163]. Weibel-Palade vesicles also store the adhesive protein vWF[164], and circulating levels of these factors are increased following trauma [165].

Hyperfibrinolysis is exacerbated by loss of fibrinolytic inhibitors[153,162,165], including alpha-2 anti-plasmin[166]and platelet dysfunction[167] (**Figure 2**). Elevated tPA activity with PAI-1 depletion is the hallmark of trauma patients with hyperfibrinolysis[55,153,162,168]. In addition, depletion of secondary tPA inhibitors (C1 inhibitor and $\alpha_1$antitrypsin), or factors that modulate inhibitor function, such as vitronectin, the cofactor for PAI-1also occurs[161]. Platelet alpha granules are the primary circulating source of PAI-1, which is secreted following stimulation and retained on the surface of activated platelets[169]. PAI-1 can also be generated in a number of cells, including endothelium. Additional factors that govern clot dissolution, including thrombin activatable fibrinolysis inhibitor (TAFI; alternatively named carboxypeptidase U; *CPB2*) and factor XIII are depleted in hyperfibrinolytic trauma patients (**Figure 9**). The antifibrinolytic function of factor XIII is conferred by cross-linking of the plasmin inhibitor, $\alpha_2$antiplasmin, into the forming fibrin matrix[170]. It has been shown that depletion of factor XIII levels to approximately 50% has a negative impact on clot stability[171]. This is important, as factor XIII circulates in complex with fibrinogen, which is also depleted in trauma[154,156].

Hyperfibrinolysis is suppressed in most trauma patients by a surge of PAI-1 that initiates at 2 hours from injury and results in the majority of patients shutdown fibrinolysis activity by 12 hours[172]. This concept, termed fibrinolysis shutdown[173], is evident in a broad range of diseases, including viral infections such as COVID-19[174]. While PAI-1 upregulation hours after injury appears to be a physiologic event, fibrinolysis shutdown that occurs within an hour of severe injury is associated with 2 to 6-fold increased mortality[175]. These patients exhibit hallmarks of prior fibrinolysis activation, including elevated D-Dimer and depletion of fibrinolytic inhibitors, yet have low systemic fibrinolytic activity on presentation to the emergency department [161]. The precise mechanism of acute fibrinolysis shutdown remains unclear. There is some evidence that the plasminogen binding protein, S100-A10, is shed into the circulation, and may associate with tPA, thereby impeding fibrinolysis[176]. Resuscitation promotes PAI-1 elevation in most injured patients, and the increase is pathologic if sustained beyond 24 hours[172].

Prior fibrinolytic activation with subsequent shutdown is associated with ongoing coagulation abnormalities, including platelet dysfunction and prolonged prothrombin time[176,177]. It remains controversial whether these patients may have shutdown fibrinolysis at the systemic level while having ongoing bleeding at the local tissue level, a phenomenon labeled as “occult” hyperfibrinolysis[176]. Regardless of terms, patients with low fibrinolytic activity, measured by viscoelastic activity and elevated D-Dimer or PAP levels, have increased mortality compared to patients with balanced fibrinolytic activity, with significantly less blood product utilization compared to patients with hyperfibrinolysis[161,176,177]. Patients in fibrinolysis shutdown tend to have delayed mortality from brain injury and organ failure, while hyperfibrinolytic patients die early from hemorrhage[9]. To add complexity, a subset of trauma patients do not generate a robust fibrinolytic response, and present to the hospital in a low fibrinolytic state, which is also associated with increased mortality[165]. Hypofibrinolysis, defined as lack of fibrinolysis activation with low fibrinolytic activity remains poorly described in trauma, but may contribute to thrombotic complications.

Ongoing work on fibrinolysis in trauma has focused on the temporal changes of fibrinolysis following injury. Most trauma patients transition to a depressed fibrinolytic state following severe injury[178]. Trauma patients who retain low fibrinolytic activity beyond 24 hours (both adults[172,178,179] and children[180]) exhibit increased mortality. This could be attributed to elevated PAI-1, which is associated with poor outcomes in sepsis, but requires further investigation in trauma. Alternative

mechanisms to inhibit fibrinolysis include activation of a persistent inflammatory state, in which neutrophil elastase has been demonstrated to reduce fibrinolytic activity[181].

[H2] Sex Dimorphism

Sex dimorphisms in coagulation have been described in humans, with females manifesting a more hypercoagulable profile[182]. As females often have less severe, and less penetrating trauma, both important TIC risk factors, isolating the independent role of sex in TIC is difficult (**Tables 1S and 2S**).

Sex's effect on postinjury morbidity and mortality has been somewhat controversial[183-186]. George et al.[187] showed that until age 50 years, men with blunt injuries had an increased death risk compared to women; among those age 50 years or older, no survival differential was noted in blunt trauma, but women with penetrating injuries had an increased mortality compared to men. Other studies across the world showed that premenopausal women have a survival advantage over men[183,188,189]. The presence of TIC seems to change this picture as a multicenter trauma study[185] found increased mortality among women presenting with TIC, independent of age.

On TIC's hypercoagulable side, we also observe disparities between women and men. Although men have higher VTE rates in their lifetime[190,191], women are at higher VTE risk during pregnancy, when using sex hormones and after ovarian stimulation. In trauma, there is controversy, with some studies showing no sex differences[192,193] in VTE rates, while others reported a higher risk in men[191]. Interestingly, the latter study accounted for post-discharge VTEs, which represented 62% of the events.

In studies with native-thrombelastography (TEG), healthy women showed faster clot initiation and stronger clots compared to men[182,194]. These differences were more pronounced in pregnant women compared to their non-pregnant counterparts[182], further suggesting that female sex hormones are involved in this protective mechanism. The Denver group[195], using rapid-TEG (with TF activation), showed that injured women had faster clot formation and strength, as well as less fibrinolysis than men, after adjustment for risk factors. Moreover, women were less likely than men to die when presenting with abnormal maximum amplitude or hyperfibrinolysis, despite being older, having longer time from injury to admission, and presenting with lower systolic blood pressure. This sex-specific hypercoagulability did not appear to increase the risk of thrombotic morbidity and it was not dependent on age. It is conceivable that epigenetic or post-translational processes due to lifetime exposure to female sex hormones could alter platelet progenitor function or cellular clotting biology, leading to a persistent hypercoagulable state during menopause.[196] The same Denver group[197], studying healthy volunteers aged 18-55 years, described that females had shorter time to clot formation, higher rate of clot propagation, and increased clot strength than males. The study showed higher levels of total and functional fibrinogen in women compared to men, but no difference in fibrinolysis. Collectively, these findings suggest that more circulating functional fibrinogen and faster coagulation activation may be involved in women's resilience to TIC. Other studies have found that men have lower fibrinogen levels as well as platelet count and function compared to women[198]. Platelets express receptors for estrogens, which might affect their function and hemostatic ability[199], and testosterone reduces agonist-induced aggregation[200]. Studies have shown conflicting results regarding platelet aggregation over the menstrual cycle[201,202]. The Denver group[203] showed that healthy men's platelets pre-treated with estradiol approximated the women's platelet activation response to platelet-activating factor, suggesting that donor sex should be considered in transfused platelets, and encouraging investigation of estradiol's therapeutic potential in TIC. Timing is also a potential factor, as serial viscoelastic tests suggest that women convert to a hypercoagulable profile postinjury earlier than their male counterparts[204].

Current postinjury resuscitation protocols are not sex-specific, theoretically exposing women to unnecessary transfusions. Given the low representation of women in trauma cohorts, a type 2 error cannot be excluded as an explanation for the lack of sex differences in transfusion requirements[185,205]. Carefully sized, inevitably large, RCTs testing sex-specific thresholds for hemostatic resuscitation, considering menstrual cycle, pregnancy and menopause, will ultimately be required.

[H1] Diagnosis, Screening and Prevention

Clinical trials have demonstrated challenges in identifying patient at risk of major bleeding, and thus clinically relevant TIC. First, there is controversy over the definition of massive transfusion. Early definitions of massive transfusion included the military description of 10 units of red blood cells (RBCs) in a 24-hour period[206]. These definitions have matured to focus on shorter intervals as detailed in the glossary[207-209]. The shorter timeframe is driven by the fact that the median time to death from bleeding is <3 hours[6,9,51], and that longer time frames lead to survivor bias (i.e., patients may die of hemorrhage early, before having the "opportunity" to receive more blood). Second, although a number of scores have been proposed, the positive predictive value remains low. Consequently, the lack of scoring systems with good predictive performance present major challenges to forecasting those who will develop TIC. As an example of the challenges faced in TIC prediction and consequently in designing clinical studies, in the large CRASH-2 international trial of tranexamic acid (TXA) for traumatic hemorrhage[210], with over 20,000 patients, only half of the patients received a blood transfusion despite being clinically assessed to be at risk for major bleeding.

Fortunately, massive transfusion rates for patients meeting trauma team activation are infrequent (3%-17%), however, massively bleeding patients are at great risk for TIC.[211-213] Identification of TIC within a cohort of massively bleeding patients can be augmented by laboratory testing. The conventional tests include a platelet count, Clauss fibrinogen level, **prothrombin time** (PT), and **activated partial thromboplastin time** (aPTT), (**Box 1**). A major limiting factor with these assays is the time to results for multiple tests, and inability to identify hyperfibrinolysis. The alternative currently is viscoelastic haemostatic assays (VHA) in a single read-out. Conventional coagulation assays can take up to 40 minutes before actionable data are available, whereas VHA provide real time data with results that can come back in half the time [211]. Some newer interpretive modifications on VHA have actionable results in 5 minutes, identifying patients at risk of massive bleeding[166,214]. Additionally, a clinical scoring system for assessing TIC, which includes subclassifications for anatomic location of injury and interventions required for bleeding control, has been proposed (**Box 1**) [215]. This scoring system correlates well with laboratory detected coagulopathy and blood transfusions but requires assessment in the OR[165]. The rapid availability and comprehensive information of VHA has led to recommendation that VHA (**Figure 10**) should replace conventional coagulation testing in TIC assessment[7]. VHA use to guide resuscitation in trauma has been associated with reduced mortality in a randomized trial[14]. The recent ITACTIC study[216] reported no differences in clinical outcomes of VHA versus conventional coagulation guided resuscitation. However, their VHA resuscitation thresholds were not based on outcomes, rather they were based on the conventional testing used in the control group, thereby creating a circular logic that resulted in the two groups being treated similarly. The conclusion from the ITACTIC study is that resuscitation based on those specific VHA thresholds did not offer benefit over conventional tests guidance, but does not offer evidence for different, outcome-based VHA resuscitation thresholds. Although the evidence in trauma is limited, substantial evidence from elective cardiac and liver transplant surgery studies provide further support for use of VHA[217].

TIC has been historically defined by PT or **international normalized ratio (INR)**, (**Box 1**) with prolongation detected in one in four severely injured patients meeting high level of trauma team activation[82,83]. Mortality in this cohort can be up to four fold higher than in similarly injured patients without prolonged PT, and the need for blood product resuscitation is significantly higher[82]. Thus, prolonged PT/INR or aPTT were proposed as clinical tests to identify TIC. However, a number of studies have subsequently documented that PT/INR may be abnormal postinjury despite normal clotting factor activity levels[205,218]. Furthermore, the exact conventional coagulation assay based definition of TIC remains a topic of debate as some investigators argue the threshold is an INR>1.2[83], while others claim it should an INR>1.5[82]. PT/INR only reflects the contribution of plasma proteins to clot formation and specifically ignores the central role of platelets. Consequently, VHAs have been adopted for the diagnosis of TIC in many countries[219-222], due to the assessment of whole blood clot formation and degradation in real time, although there has been criticism of assay reproducibility in older versions of VHA devices and its ability in measuring hyperfibrinolysis[296]. Viscoelastic evidence of decreased clot strength has repeatedly been associated with massive transfusion and increased mortality in trauma[223-225], although there is discordance on specific thresholds defining hyperfibrinolysis. Indeed, Vigneshwar et al. showed that such cutoffs should not be fixed, but combined with clinical signs of injury severity and shock.[226]

Given the vast array of coagulation changes in trauma patients, defining TIC with a single laboratory measurement is imprecise. TIC is a complex process that involves the endothelium, platelets, circulating coagulation factors, and the immune system[21,227], and no single assay or set of assays available to date effectively integrate measurement of the critical coordinated events involved in vascular homeostasis. Ex vivo laboratory assays to assess coagulation fail to account for theese important factors and are subject to limitation such as the use of buffers for collection that neutralize acidosis. Viscoelastic identified hyperfibrinolytic phenotypes are frequently associated with early mortality rates exceeding 50%[9,153,158], while fibrinolysis shutdown is associated with delayed mortality[160] Importantly, the findings of coagulation testing are similar in both pediatric patients and adults, with principal component analysis detecting similar phenotypes of TIC, and VHA predicting outcomes in a similar manner in children[228] as in adults. Even in the setting of an abnormal laboratory test, the clinical status of the patient ultimately drives decision making. Abnormal laboratory results need not be corrected with blood products in a patient with no clinical signs of coagulopathy and surgical/interventional hemostasis.

TIC becomes vastly more complex following resuscitation. The prior sections have focused on early TIC, which is mostly an innate coagulation response to tissue injury and hemorrhagic shock. However, with resuscitation, fluid administration, blood products, and hemostatic agents result in potential secondary coagulopathies as well as hemodilution, acidosis, and hypothermia[21]. Further, in the event of uncontrolled bleeding due to lack of mechanical control, this coagulopathy is exacerbated. Following resolution of hemorrhage and hypoperfusion, most patients transition from an early hypocoagulable to a late hypercoagulable state[229]. Late hypercoagulable TIC presents a new set of challenges in clinical management focused on prevention of thrombotic complications[21]. The specific laboratory definition of late hypercoagulable TIC remains even more elusive, but several studies have identified increased clot strength and fibrinolysis shutdown, as measured by VHA, following resuscitation as a risk factor for venous thromboembolism[230-232] and stroke[233]. Trending VHA during hospital admission[180] has identified changes in TIC phenotype associated with thrombotic complications, however, the measures to mitigate late TIC are presently focused on best practice of hemostatic resuscitation with blood products, and thromboprophylaxis.

[H1] Management

[H2] Prehospital care

The initial management of TIC focuses on preventing progression to hemorrhagic shock by arresting the bleeding, and restoring circulating blood volume, thereby, attenuating the effects of acidosis on coagulation. Efforts have been made to make the public aware of strategies such as tourniquets ("Stop the Bleed" and "STOP the Bleeding Campaign")[234,235] and direct compression of bleeding wounds to slow hemorrhage. Prehospital health care providers also initiate resuscitation of the critically ill trauma patient with to increase intravascular volume to preserve organ perfusion. The fluids administered in the prehospital setting to increase the effective circulating volume can help but potentially harm the patient. Large volume crystalloid resuscitation can increase the blood pressure, but may also exacerbate coagulopathy and "pop the clot"[236] if blood pressure is raised too rapidly. Permissive hypotension with low volume crystalloid administration has been demonstrated to be effective for the management of trauma patients in the prehospital setting[237]. High volumes of crystalloid resuscitation have been associated with hyperfibrinolysis upon presentation to the hospital[158] partially through dilution of antifibrinolytic circulating proteins[238], in addition to being independently associated with morbidity [239]. A permissive hypotensive strategy in actively bleeding patients is advocated in trauma patients until definitive bleeding control can be achieved, but the optimal level of hypotension remains to be established, particularly with TBI.

Additional adjuncts in the prehospital setting include the transfusion of blood products. Prehospital plasma resuscitation reduces mortality in patients who undergo helicopter transportation[6]. However, plasma first resuscitation in an urban setting with short transportation time did not reduce mortality and was associated with a prolonged INR[5]. In a post-hoc analysis of two recent clinical trials of prehospital plasma with harmonized inclusion criteria, the benefit of prehospital plasma appeared to be limited to those with transport times exceeding 20 minutes[240]. Ongoing work is evaluating the potential role of

lyophilized plasma in the prehospital setting, as it overcomes the logistical challenges of de-thawing plasma in the mobile setting. Efforts are also being made to evaluate the use of whole blood as a prehospital resuscitation strategy, which has been proven to be feasible[241], but impact on coagulopathy remains to be determined [242].

TXA has been shown to reduce mortality in a large trauma study [210], and therefore has been implemented in some prehospital systems. But the optimal target group remains unclear. Recently, two large randomized clinical trials of prehospital TXA have been reported. The Study of Tranexamic Acid during Air and ground Medical Prehospital transport (STAAMP) [243] trial was a phase-3, multicenter RCT of TXA versus placebo, given within an estimated 2 hours postinjury in the prehospital setting to patients with hypotension or tachycardia. The study demonstrated no significant difference in the primary outcome of 30-day mortality (9.9% placebo, 8.1% TXA, p=0.17). However, in a pre-planned subgroup analyses, patients with severe shock (systolic blood pressure <70mmHg) who received TXA within one hour postinjury had a statistically significant reduction in 30-day mortality. Similarly, the Prehospital TXA for TBI Trial [244] was a randomized, double blind, multicenter phase-2 trial designed to assess safety and efficacy of TXA versus placebo in patients with moderate to severe TBI but without hemorrhagic shock. This study evaluated TXA given within 2 hours postinjury in the prehospital setting as either a 1g TXA bolus with in-hospital 1g infusion, 2g bolus followed by in-hospital infusion, or placebo with a primary outcome of favorable neurologic function at 6 months. Neither dosing strategy of TXA was found to be superior, with no statistically significant difference in the primary outcome nor 28-day mortality when dosing strategies were combined in the analysis. When assessed independently as a secondary analysis, however, the 2g prehospital bolus was associated with a trend towards reduced mortality[243], although this came at the expense of an increase in the rate of seizures from 2% (placebo) to 6% (2-g bolus). However, RCTs on TXA have not randomized patients based on their fibrinolytic status.

The potential risk of VTE with TXA has been a topic of debate. Retrospective studies in both civilian[245] and military medicine[246] suggest an association with increased VTE rates, although these studies were limited by their retrospective design. The use of TXA as an anti-fibrinolytic could theoretically increase the incidence of postinjury fibrinolysis shutdown, and the observation that late (>3 hours postinjury) TXA is associated with death[247] strongly indicates that TXA should be administered early, and likely not given to patients with evidence of fibrinolysis shutdown[248,249] A small single-center randomized trial in severely injured trauma patients suggested a dose-dependent increase in a composite outcome of thrombotic events in patients receiving TXA (% of thrombotic events, placebo 12%, 2g TXA 27%, 4g TXA 32%, p=0.05)[250]. The recent HALT-IT trial [251] of TXA in gastrointestinal hemorrhage indicated a significant increase in VTE with a 4g dose of TXA given over 24 hours (placebo 0.4% vs TXA 0.8%, Relative Risk 1.85; 95% CI: 1.15-2.98). In contrast, the CRASH-2[210] and CRASH-3[252] trials randomized tens of thousands of patients at risk for hemorrhage postinjury to TXA vs placebo, and neither study demonstrated a VTE increase. This aligns with the observation of safety and low VTE rates in randomized trials of TXA in other bleeding conditions such as post-partum hemorrhage[253]. CRASH-2 and CRASH-3 have been criticized for reporting VTE rates substantially lower than most studies, possibly due to the low rate of patients who actually required transfusion. However, the STAAMP and Prehospital TXA for TBI trials had substantially higher VTE rates than those reported in the CRASH studies.[254]

[H2] Hospital care

Patients who arrive to the hospital in overt hemorrhagic shock warrant empiric blood product resuscitation to restore circulating blood volume and thereby attenuate the development of worsening coagulopathy. This includes a high ratio of plasma to RBCs to attenuate exacerbation of coagulopathy[206]. The exact ratio of RBCs to plasma remains debated but should be at minimum 2:1. The only RCT evaluating these ratios demonstrated no benefit in survival with 1:1 over 2:1[42], but suggested a shorter time to hemostasis in the higher ratio group. This study also included early platelet transfusions in the 1:1 arm, which has been associated with improved outcomes in trauma in a retrospective study[255]. These improved outcomes with high ratios of these products are limited to trauma patients undergoing a massive transfusion, and there is evidence that the non-massively transfused trauma patients may be harmed by using these blood products. High ratios of fibrinogen/**cryoprecipitate** (**Box 1**) to RBC have also been advocated to decrease trauma mortality[256], but await the results of ongoing RCTs. The new proposal (but historic practice) to high ratio resuscitation is the use of whole blood[257]. Low anti-

A and anti-B titer, group 0 whole blood (LTOWB) was the standard for trauma resuscitation until blood component separation in the early 1980s, and has been shown to be feasible and safe as initial fluid in the United States[258,259]. In a single center study of injured adults, the use of LTOWB has been associated with reduced transfusion volumes and increased in survival compared to component therapy[260]. The safety of LTOWB has been confirmed also for pediatric patients presenting with hemorrhagic shock. If empiric ratios of RBC and plasma are used to resuscitate massively bleeding patients, cryoprecipitate/fibrinogen and platelets should be initiated if the patient has begun to receive more than four units of RBCs before laboratory results are available[209].

Bicarbonate should be given only if severe acidosis persists despite resuscitation, as bicarbonate therapy has been shown to be ineffective or harmful in general. Its harm is due to excess HCO_3-derived CO_2, which is very soluble across cell membranes, causing a cellular respiratory acidosis not reflected in arterial pH or $PaCO_2$ measurements[261,262].

All trauma patients with major bleeding need ongoing coagulation assessment regardless of their transfusion strategy, as demonstrated in a RCT of goal directed resuscitation, guided by VHA, in which mortality was reduced by almost 50% in trauma patients in whom a massive transfusion protocol was activated[14]. Goal directed resuscitation targets the patient's specific coagulation phenotype, with the objective of achieving a normal coagulation profile without excessive blood component use, which has been associated with the best outcome[263]. Algorithms for specific hemostatic adjuncts including plasma, cryoprecipitate/fibrinogen, platelets, and TXA can be directed with VHA or equivalent hemostatic assays [264-266](**Figure 11**). A recent meta-analysis of VHA supports this concept as pooled randomized control data in patients undergoing VHA-based emergency resuscitation consumed less plasma and platelets with an associated reduction in post-operative mechanical ventilation days[217]. However, a reliable test to ascertain when to administer platelets in trauma patients is lacking. Impairment in platelet-dependent hemostasis characteristic of TIC do not predict the need for platelet transfusion, nor do platelet transfusions reverse these impairments[122,123,267]. Ultimately, the clinical status of the patient should

While no specific studies have evaluated the timing of coagulation assessment in trauma, the dynamic nature of resuscitation warrant early and repeated monitoring until hemostasis is achieved and a return to balanced resuscitation is warranted if hemostasis is lost.

Trauma patients who present to the hospital with occult bleeding but who are physiologically compensated pose a different challenge in resuscitation. A common source for occult bleeding is solid abdominal organ injury, which can be managed predominantly with non-operative interventions. Targeted resuscitation of these patients is an important approach as most transition to a hypercoagulable state by 24-48 hours.[230,231] .

TBI poses unique challenges in management of coagulation. Unlike abdominal and thoracic cavities that can accommodate moderate amounts of bleeding, the fixed space in the calvarium warrants a more aggressive approach in obtaining timely hemostasis. The CRASH-3 study identified a survival benefit in early TXA in mild to moderate TBI, but no benefit in severe head injury [268]. The protective effect of TXA in TBI, however, remains unclear and may be more related to countering inflammation than improving hemostasis. TBI represents a unique phenotype of TIC, however the resuscitation and management of TBI associated TIC are largely similar to coagulopathy associated with non-TBI injury. One major challenge in TBI associated TIC is the use of pharmacologic prophylaxis against VTE. The transition to hypercoagulability after injury poses a major clinical challenge, with high VTE rates noted in patients who have TBI. The decision to initiate anticoagulation to prevent postinjury clotting and thrombotic complication needs to be weighed against the risk of exacerbating bleeding, particularly with associated brain injury. Early VTE prophylaxis in TBI patients has been associated with a reduction in VTE incidence without worsening of intracranial hemorrhage when started after a stable head CT[269]. Low-molecular weight heparin has been shown to be superior to unfractionated heparin in this cohort, with improved survival and fewer thromboembolic complications[270]. Due to patient immobility and the hypercoagulable state, thromboprophylaxis is administered as soon as possible after bleeding risk has subsided and individual patient factors must guide the choice of UFH or LMWH[271,272].

Importantly, global variations exist with respect to resuscitation strategies (**Box 3**). As an example, the European guidelines[157] on the management of major bleeding and coagulopathy following trauma strongly emphasize that early resuscitation with cryoprecipitate or fibrinogen concentrate to overcome rapid depletion of fibrinogen in trauma patients. This varies from a largely "plasma first" and platelets approach to hemostatic resuscitation in the United States. Further complicating this issue is the lack of stored blood and its components in many parts of the developing world, making global recommendations for management impractical.

[H1] Quality of Life

Data from the World Health Organization Global Burden of Disease and Injury study show that, despite sizeable gains since the 1990's, injury remains a substantial cause of morbidity around the world[273]. Few studies provide information on the long-term outcomes of TIC's hypocoagulable phenotype. The Trauma Recovery Project (TRP) is a large prospective study of injured patients without serious head injury that assesses QOL as well as functional and psychological (depression; posttraumatic stress disorder, PTSD) outcomes.[274,275] Adults showed over 75% prevalence of postinjury functional limitation at 12- and 18-month follow-up. Depression was present in 60% of the patients at discharge and 31% at 6-month follow-up. In TRP subsequent studies, women were more likely than men to have poor QOL at 6-, 12- and 18-month follow-up[274,276]. The TRP in Adolescents 1999-2002 study[277], which focused on injured adolescents without serious brain trauma, showed acute stress disorder (ASD) was present in 40% upon discharge and was associated with large QOL deficits at 3-, 6-, 12- and 24-month follow-ups. Long-term PTSD's rate was 27%[278]. Winthrop et al.[279] in a longitudinal study of 156 children with blunt trauma (but no head/ spinal cord injuries) showed that at 6 months, the physical scores remained lower than age-matched norms.

In the CONTROL international RCT of activated Factor VII,[280] including severely injured adults with refractory bleeding but no severe brain injuries, survivors reported very poor QOL three months postinjury, with over 70% reporting moderate/extreme difficulties in usual activities, pain/discomfort and mobility limitations. Over half of the patients reported self-care problems and anxiety/depression. Mitra et al. [281] in an Australian trauma center assessed **Glasgow Outcome Score-Extended (GOSE)**[1] (**Box 1**) at 6 and 12 months, in adults who required massive blood transfusion postinjury (patients with TBIs were not excluded) and demonstrated that massive transfusion was independently associated with unfavorable outcomes among survivors at 6 months postinjury.

The hypercoagulable extreme of TIC, prevalent in patients who survive the initial resuscitation, is linked to MOF and ARDS, as well as macro-thrombotic complications such as VTE[9,165], all associated with prolonged hospitalization. Patients requiring prolonged intensive care develop a state of chronic critical illness (CCI, defined as ≥ 14 ICU days with persistent organ dysfunction)[282,283], which is associated with dismal long-term outcomes in series of non-TBI trauma patients[282,284]. Gardner et al.[284], studying non-TBI subjects, showed that CCI subjects at 3-, 6- and 12-month follow-up had significantly lower physical function and QOL than their counterparts who rapidly recovered. Mira et al.[282] followed 135 adult blunt trauma patients with hemorrhagic shock who survived beyond 48-hours postinjury, of whom 19% developed CCI; these patients were more likely to require long-term care and, at 4-month follow-up, scored lower in general health measures.

VTE's incidence postinjury depends on whether there is routine surveillance (versus symptom-driven diagnosis) and the use of thromboprophylaxis. A comparison of two US trauma centers showed that serial VTE surveillance via ultrasound detected deep venous thrombosis (DVT) in 9% of patients admitted for > 48 hours, while surveillance of only symptomatic patients showed a smaller, 2% DVT incidence, despite similar thromboprophylaxis protocols[285]. Pulmonary embolism (PE) was diagnosed in 0.4% of these patients, similar to another US multicenter investigation[286]. Analyses of the US National

Trauma Data Bank showed in-hospital VTE rates around 1%[192,287,288]. In a Switzerland trauma center, VTE's rate was 7%-10%[289], while in Germany, it was reported to be 2%. Military data suggest a higher VTE incidence than in civilians (2 to 22%)[290-292]. A review of long-term functional outcomes after an acute PE showed that more than half of the patients reported dyspnea and poor physical performance[293] with rates of chronic thromboembolic pulmonary hypertension as high as 3.8% at two years[294]. The incidence of post-thrombotic syndrome, a chronic debilitating consequence of acute DVT, has been estimated to be 20-50% even when appropriately treated[295].

[H1] Outlook

The investigation of the fundamental mechanisms of TIC has been pursued for over a 100 years, beginning with the work of Walter B. Cannon in World War I[296]. While there have been substantial insights, Mario Stefanini's words in his address to the New York Academy of Medicine in 1954 remain applicable: "The ponderous literature on the subject of hemostasis could perhaps be considered a classical example of the infinite ability of the human mind for abstract speculation. For several years, the number of working theories of the hemostatic mechanisms greatly exceeded and not always respected the confirmed experimental facts. In recent years, however, the revived interest in this field has led to an accumulation of new findings, which has been almost too rapid for their orderly incorporation into a logical working pattern" [297]. While Stefanini's words apply to today, we have made substantial progress over the past three decades stimulated by the introduction of the cell-based model of hemostasis, and further inspired by the confirmation that uncontrolled cavitary bleeding was the leading cause of death in the War in Iraq[3]. Despite much knowledge gained, there are a myriad of gaps to be addressed.

Perhaps most conspicuous is a clinical definition of TIC, and further distinguishing between the dynamic early/hypocoagulable versus late/hypercoagulable based on a mechanistic foundation. The initial proposal of using PT/INR to define early TIC has been subsequently questioned, and rather considered a biomarker of injury. Clinical coagulation scoring systems have been developed, but these are relatively insensitive unless based on cavitary exposure in the operating room. Definitions of massive transfusion, e.g., > 4 RBC units or death from bleeding in the first hour postinjury has been suggested but does not capture the impact of TIC on TBI. Additionally, multiple TIC phenotypes exist, and these need to be defined to optimize goal-directed therapy. As a corollary, of those patients with refractory early TIC, how do we distinguish between those patients who are "dying because they are bleeding" from those "bleeding because they are dying?"

A number of mechanistic hypothesis have been proposed to drive early TIC, but definitive evidence remains elusive for many. Notably among the controversial proposals are the roles of thrombin-induced activation of protein C and heparan sulfate released from the disrupted endothelial glycocalyx. Shock and tissue ischemia appear to dominate in early TIC, but the mediators remain to be identified, including metabolites. The contributing role of tissue injury is also unclear, and may be critical in determining early fibrinolytic phenotypes. Interestingly, isolated shock or TBI are not associated with a pronounced TIC but, in combination with tissue injury, provoke a conspicuous early TIC. In fact, the mechanisms driving TIC from TBI appear to be unique and need to be elucidated. There is clear evidence of cross-talk between inflammation and coagulation but the direct links remain to be elucidated.

Early TIC has been suggested to result from a combination of inadequate thrombin generation, platelet dysfunction, fibrinogen depletion, and hyperfibrinolysis. However, the relative contribution of these abnormalities remains unclear, and some of these coagulation aberrations may be biomarkers rather than critical mechanistic drivers. While thrombin generation has been described as accelerated following trauma, recent evidence indicates it is depressed in patients requiring a massive transfusion[22]. On the other hand, excessive thrombin generation has been associated with VTE. What constitutes appropriate thrombin in the evolution of TIC is unknown. Platelet dysfunction has been well documented following severe injury, but its etiology, mechanism, and role in early and late TIC remain unclear. The findings of dysfunction in circulating platelets may represent the platelets that have already functioned, rather than the hemostatic capacity of the platelet reserves in the local injury environment. Fibrinogen is the first circulating coagulation protein decreased following severe injury, but what

critical level warrants replacement remains to be established. The overlapping roles of platelets and fibrinogen in clot formation compounds the issue; i.e., one of these components may compensate for a deficiency in the other. Finally, the impact of fibrinolysis phenotypes in early and late TIC remains debated. While hyperfibrinolysis may compromise hemostasis, shutdown may contribute to later ARDS and MOF. These observations continue to raise the question of whether TXA should be used selectively following injury, particularly in the USA.

The endothelium is the "black box" in TIC. Endothelial activation has been invoked as a dominant feature of early TIC, but this is based on the presence of shed biomarkers, rather than real-time assessment of endothelial behavior. The endotheliopathy of trauma, and more specifically barrier breakdown, has been documented *in vitro* and *in vivo* but the relationship to TIC remains speculative.

The optimal coagulation platform to assess early and late TIC has yet to be developed. The shortcomings of traditional plasma-based tests (PT/INR, aPTT) have been recognized, and they have been replaced by viscoelastic hemostatic assays (TEG and ROTEM). Although TEG and ROTEM whole blood assays reflect the various phases of clot formation, they are not performed on activated endothelium with physiologic shear stress. Furthermore, these devices are not reliable to ascertain platelet functional capability and their precision in measuring fibrinolysis is debated[298]. Microfluidic devices have been employed for research and will likely emerge for clinical use soon. Consequently, at this time, we are unable to accurately determine the timing and specific blood products required to avert a massive transfusion or progressive TBI. We are currently unable to clearly discern the transition from hypocoagulability to hypercoagulability, and this state may differ in the arterial (high shear stress) versus venous (low shear) systems. Consequently, we continue to debate when to initiate VTE preventive therapy and the optimal preventive agents.

Ultimately, the goal of personalized medicine of the injured patient at risk for TIC is to deliver the right product(s) at the right time to the right patient. However, our current understanding of the pathophysiology of TIC remains incomplete despite intense research focus, and compounded by limitations in diagnostic testing, rendering current clinical decisions imprecise. For example, there are disparate views across the Atlantic as to whether early platelets or fibrinogen are optimal. Additional questions include whether cryoprecipitate is superior to fibrinogen concentrates, whether PCCs are equivalent to FFP, and whether TXA should be administered selectively to trauma patients based on injury pattern. While initial administration of low-titer type O-positive whole blood (LTOWB) is attractive, returning to stored whole blood throughout resuscitation is not consistent with our knowledge of the varied phenotypes of TIC.

Figure Legends

- **Figure 1: Phenotypes of Trauma Induced Coagulopathy**
  Physiologic clot formation and degradation represent a delicate balance of prothrombotic/antithrombotic and fibrinolytic/antifibrinolytic processes. Consequently, there are distinct early and late phenotypes resulting from tissue injury, shock, traumatic brain injury (TBI) as well as individual response to these insults. Adapted from From Moore EE, Moore HB, Chapman MP, Gonzalez E, Sauaia A. Goal-directed hemostatic resuscitation for trauma induced coagulopathy: Maintaining homeostasis. The Journal of Trauma and Acute Care Surgery. 2018 Jun;84(6S Suppl 1):S35-S40. DOI: 10.1097/ta.0000000000001797.

- **Figure 2: Mechanisms of Trauma Induced Coagulopathy**
  Progress in understanding the pathogenesis of TIC has been inspired by the revolutionary concept of the cell-based model of coagulation that emphasizes the fundamental role of platelets as a platform for clotting factor assembly, thrombin generation and incorporation of fibrin to form a hemostatic plug on damaged endothelium. While there are a number of hypotheses for the driving mechanisms, tissue injury and shock synergistically activate the endothelium, platelets and the immune system to generate an array of mediators that reduce fibrinogen, impair platelets function, and compromise thrombin generation ultimately resulting in inadequate clot formation for hemostasis. Enhanced fibrinolysis via plasmin generation further compromises hemostatic capacity. These defects are accentuated by ongoing blood loss, hemodilution, metabolic acidosis, and hypothermia (the lethal triad).

- **Figure 3: Distribution of All Hemorrhagic Deaths Over Time in Three Randomized Controlled Trials**
  - PROPPR [4,42](n = 680) Time zero= randomization in-hospital; Entry criteria: > 1 unit of blood product and Assessment of Blood Consumption score>1 or physician's prediction of massive transfusion need
  - PAMPer (n = 501)[6] Time zero=scene arrival; Entry criteria: Air transported and Systolic Blood Pressure (SBP)<70mmHg or SBP <90mmHg + Heart Rate (HR)>108bpm
  - COMBAT (n = 144) [5]Time zero=dispatch; Entry criteria: Ground transported and SBP<70mmHg or SBP <90mmHg + HR>108bpm
  - Note: Among patients requiring $\geq$ 1 unit of red blood cells/24 hours, 85% of the hemorrhagic deaths in PAMPer and 50% in COMBAT occurred $\leq$6 hours.

  Adapted from Sauaia A, Moore EE, Wade C, Holcomb JB. Epidemiology of Hemorrhagic Deaths. In: Moore HB, Neal MD, Moore EE, eds. Trauma Induced Coagulopathy. 2nd. ed.: Springer; 2020

- **Figure 4: Platelet and Endothelial Interactions**

  In health, endothelial cell architecture projects beyond cell membranes via a glycocalyx of polysaccharides linked to membrane and trans-membrane proteoglycans (protein cores attached to glycosaminoglycans), fortified with soluble glycoproteins that coordinate coagulation and immune functions. The glycocalyx provides cytoprotection, membrane integrity, and anti-apoptotic anti-thrombotic signaling. Extracellular proteases, like metalloproteases (MMPs), cleave glycocalyx ectodomains, and expose neutrophil adhesion receptors for neutrophil binding and chemo-attractant and cytokine release. Clot formation relies on platelet plug construction (primary hemostasis) by thrombin-stimulated platelet adherence to exposed extravascular matrices via tissue factor (TF), von-Willebrand Factor (vWF), collagen, and protein structure. Thrombin-stimulation and platelet glycoprotein VI-collagen binding induce calcium mobilization, disc to sphere structure, procoagulant factor degranulation, and glycoprotein IIb/IIIa receptor conformational change to accept fibrin binding. Additionally, platelets control local fibrinolysis via degranulation of plasminogen activator inhibitor-1 (PAI-1) and antiplasmin-2 rich alpha-granules to maintain prothrombotic, antifibrinolytic clot architecture. Secondarily, activated platelets recruit leukocytes to local environments. Further, via reciprocal trophogenesis, platelets promote endothelial stability and angiogenesis in return for endothelial release of factors promoting platelet-dependent hemostasis like vWF, and of cytokines signaling megakaryocytes to produce platelets.

- **Figure 5: Cell-Based Model of Coagulation**

  Initiation occurs on TF-bearing cells as the FVIIa/TF complex activates FX. Fxa binds to its cofactor, Fva, and activates small amounts of thrombin. Thrombin generated on the TF-bearing cell amplifies the procoagulant response by activating additional coagulation factors and platelets. The large burst of thrombin required for formation of a fibrin clot is generated on platelet surfaces during the propagation phase. Adapted from Hoffman M, Monroe DM. Impact of Non-Vitamin K Antagonist Oral Anticoagulants From a Basic Science Perspective. Arterioscler Thromb Vasc Biol. 2017;37(10):1812-1818. doi:10.1161/ATVBAHA.117.306995

- **Figure 6: Clotting Factor Cascade**

  Fibrin formation via the proteolytic clotting factor cascade represents a delicate balance of prothrombotic and antithrombotic mediators. The extrinsic or tissue factor cascade is initiated by binding of TF and Factor VIIa stimulating the activation of Factor X to complex with Factor Va (prothrombinase), while the intrinsic or contact activation pathway is provoked by a negatively charged surface, prekallikrein, high-molecular weight kininogen or Factor XII that activate Factor XI and similarly results in the assembly of prothrombinase complex in the common pathway. The extrinsic and intrinsic systems are not redundant but rather participate synergistically in thrombin formation. Adapted from Gando, S., Levi, M. & Toh, CH. Disseminated intravascular coagulation. Nat Rev Dis Primers 2, 16037 (2016). https://doi.org/10.1038/nrdp.2016.37

- **Figure 7: Multifunctional Roles of Thrombin**
  Once activated by the coagulation cascade, thrombin can function in procoagulant, anticoagulant, antifibrinolytic, and pro/anti-inflammatory pathways. The serin protease thrombin stimulates multiple procoagulant and anticoagulant (protein C) pathways and inhibits fibrinolysis (TAFI) and is a strong platelet activator (PAR). Moreover, thrombin is involved in pro- and anti-inflammatory pathways. Adapted from Crawley JT, Zanardelli S, Chion CK, Lane DA. The central role of thrombin in hemostasis. J Thromb Haemost. 2007 Jul;5 Suppl 1:95-101. doi: 10.1111/j.1538-7836.2007.02500.x. PMID: 17635715.Supp 1) 95-101)

- **Figure 8**: **Fibrin Formation**
  Thrombin-catalyzed conversion of soluble fibrinogen to insoluble fibrin matrix is central to hemostasis. Fibrin polymerization is initiated by cleavage of the fibrinopeptides A and B located in the central E-domain. These fibrinopepides mask complementary polymerization sites in the gamma-C and beta-C regions of the D-domains. Two fibrin monomers interact with each other in a half-staggered manner.

- **Figure 9**: **Regulation of Fibrinolysis**
  PAI-1 is the primary inhibitor of tPA, its back up inhibitor is C-1 esterase inhibitor. Depletion of multiple inhibitors of fibrinolysis after fibrinolytic activation in trauma beyond PAI-1 includes a wide range of proteins that can directly bind PAI-1 (alpha-1 antitrypsin) or modulate its activity (vitronectin). Platelets also provide an abundant source of local PAI-1 with alpha degranulation. Additional regulators of clot degradation including thrombin activated fibrinolysis inhibitor (TAFI) and factor XIII. Factor XIII plays a critical role in clot stability to fibrinolysis by cross-linking plasmin's main inhibitor into growing fibrin polymers. Adapted from Urano T, Suzuki Y. Thrombolytic therapy targeting alpha 2-antiplasmin. Circulation 2017; 135: 1021–3.

- **Figure 10: Viscoelastic Hemostatic Assays**
  Thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are currently the most widely used viscoelastic assays to assess and manage TIC. They have similar measurements to reflect the phases of clot formation and clot degradation. The respective measurements for TEG and ROTEM are: the reaction (R)-time and clotting time (CT), time until clot firmness amplitude of 2mm; the coagulation (K)-time and clotting formation time (CFT), time between 2 and 20 mm clot firmness amplitude; the alpha angle for both, tangent line between baseline and 2 mm point; maximum amplitude (MA) and maximum clot firmness (MCF), maximum clot firmness achieved; and lysis at 30 min after MA (LY 30) and residual clot firmness at 30 min after CT (LI 30). Adapted from Harr, J.N., Moore, E.E., Chin, T.L. et al. Viscoelastic hemostatic fibrinogen assays detect fibrinolysis early. Eur J Trauma Emerg Surg 41, 49–56 (2015)

- **Figure 11: Examples of Goal-Directed Algorithm For Hemostatic Resuscitation.**
  These algorithms are examples of TEG or ROTEM based approaches: **11a.** North American example; **11b.** European example (adapted from Görlinger et al. Reduction of Fresh Frozen Plasma Requirements by Perioperative Point-of-Care Coagulation Management with Early Calculated Goal-Directed Therapy. Transfus Med Hemother. 2012 Apr;39(2):104-113. doi: 10.1159/000337186. Epub 2012 Mar 8. PMID: 22670128)

Box 1. GLOSSARY

1. **Activated Partial Thromboplastin Time (PTT):** PTT is a conventional coagulation assay that measures the clotting activity of the intrinsic pathway cascade. It tests the function of all clotting factors except factor VII (tissue factor) and factor XIII (fibrin stabilizing factor). It is often used to monitor patients' response to unfractionated heparin infusion, to target therapeutic anticoagulation.

2. **Auto-dilution**: shifts of interstitial fluid into the vascular compartment in response to hemorrhagic shock, which may impair hemostatic capacity.
3. **Bleeding-control bundle-of-care**: accurate identification of the bleeding patient; damage control resuscitation; hemostatic techniques with tourniquets, pelvic binders, hemostatic dressings; resuscitative endovascular balloon occlusion of the aorta; thrombelastography coagulation monitoring; tranexamic acid for significant hyperfibrinolysis; decreased time to operating room and interventional radiology; goal-directed resuscitation with blood products.
4. **Cryoprecipitate**: plasma-derived blood product for transfusion that contains fibrinogen (factor I), factor VIII, factor XIII, von Willebrand factor, and fibronectin.
5. **Damage control resuscitation** (DCR): DCR consists of limited crystalloid fluid, permissive hypotension and administration of balanced blood components in severely injured patients to attenuate TIC.
6. **Damage control surgery (DCS)**: DCS is completing essential operative maneuvers; i.e., control of mechanical bleeding, shunting critical arteries, controlling gastrointestinal spillage, and packing bleeding sites in patients manifesting TIC due to ongoing shock, and returning to the operating room to complete definitive reconstruction after patient stabilizes.
7. **Glasgow Outcome Score-Extended (GOSE):** global scale for functional outcome that rates patient status into eight categories (death, vegetative state, lower severe disability, upper severe disability, lower moderate disability, upper moderate disability, lower good recovery, upper good recovery
8. **Goal-directed resuscitation**: hemostatic resuscitation with blood components guided by viscoelastic hemostatic tests directed at normalizing coagulation.
9. **Massive transfusion**: several definitions exist. The most frequently used is >10 red blood cell (RBC) units/24 hours, although this definition is subject to substantial survivor bias (i.e., persons who died before 24 hours may not have the "opportunity" to receive 10 units). Other definitions include: 1) the critical administration threshold (CAT: ≥3 RBC units/hour in the first hour or in any of the first 4 hours from arrival), 2) > 4 RBC units or death in the first hour postinjury, which has the advantage of minimizing survivor bias; and 3) > 4 RBC units within the first hour, is also known as the resuscitation intensity (RI) definition.
10. **Potentially preventable trauma deaths**: (1) the injury must be survivable, (2) the delivery of care is suboptimal, and (3) the error in care must be directly or indirectly implicated in the death of the patient.
11. **Primary and secondary hemostasis**: Primary hemostasis refers to platelet aggregation plug formation on an injury site, while secondary hemostasis refers to the deposition of insoluble fibrin, generated by the proteolytic coagulation cascade, into the platelet plug, which forms a mesh that is incorporated into and around the platelet plug.
12. **Prothrombin time (PT) and International Normalized Ratio (INR):** PT is a conventional coagulation assay that evaluates the extrinsic and the common pathways of the coagulation cascade. The PT result (in seconds) on a normal individual varies between different types and batches of manufacturer's tissue factor used. The INR was devised to standardize the results. Manufacturers assign an International Sensitivity Index (IST) for their tissue factor and the INR is calculated as (PT test/ PT normal) ^{IST}
13. **Viscoelastic hemostatic assays**: assays based on the whole blood; measure change in viscoelastic properties of the whole blood during clot formation, strength and dissolution. The most commonly used devices are thrombelastography (TEG) and rotational thromboelastometry (ROTEM).

Box 2: Critical Appraisal of Trauma-induced Coagulopathy

A critical appraisal of the TIC literature is essential before applying the findings to other patients or research agendas. The PICOTS (Population/Patients, Intervention, Comparator, Outcome, Time, Setting/System) framework is a useful start:

1) **Population**: the population studied often varies; massive transfusion is a frequent criterion for inclusion, yet it is defined variably, which hampers comparisons across studies, and it is subject to survivor bias. Traumatic brain injury (TBI) has substantial confounding and/or modifying effects on risk factors and outcomes of TIC.

2) **Intervention**: it is absolutely critical that authors report (and readers pay attention to) when therapy started related to the injury, arrival of rescue, hospital admission, initiation of transfusions, bleeding mechanical control, as well as other events that modify TIC's risk and/or outcomes.

3) **Comparator**: in observational studies, obtaining comparable study groups (for example, by adjustment for confounders though multivariate or propensity score matching) is a challenge. In hemorrhagic shock, minutes of difference between the study groups can be of significance.

4) **Outcomes**: the definition of TIC varies, with contemporary studies often relying on viscoelastic tests, which, often have inconsistent cutoffs to define abnormalities. Such cutoffs should not be fixed, but combined with clinical signs of injury severity and shock.[226]

5) **Time**: the timing when TIC is measured (prehospital, upon hospital admission, before or after transfusions and hemorrhage control, during ICU admission) is critical for an accurate interpretation.

6) **Setting**: thus urban trauma systems with short transport times may experience different rates of TIC than less organized systems, austere environments or settings with long transport times (e.g., rural areas, air-transported patients). Indeed, in the COMBAT[5] and PAMPer[6] randomized controlled trials, patients with transport times longer than 20 minutes were more likely to experience benefit from prehospital plasma[240].

Box 3: Variations in TIC diagnosis and management

	Approach A (favored in North America)	**Approach B (favored in Western Europe)**
Restoring lost volume	Balanced blood components	Balanced crystalloid solutions with vasopressors if needed
Goal directed resuscitation	Yes, with VHA	Yes, with either conventional or VHA coagulation tests
Plasma vs Fibrinogen	Plasma used for volume expansion; Cryoprecipitate used to increase fibrinogen	Fibrinogen used to correct factor deficiency
Balanced blood components	Typically RBC:Plasma: Platelets 1:1:1 or Plasma:RBC 1:2 used to initiate resuscitation	Plasma:RBC ratio of at least 1:2; Platelets and PCC based on laboratory testing
Low titer O negative whole blood	Considered instead of RBC:Plasma: Platelets 1:1:1 when available	Not used
Pre-emptive tranexamic acid	Long transport, austere environments	Recommended

VHA: viscoelastic hemostatic assays; RBC: red blood cells; PCC: prothrombin complex concentrate (Factors II, VII, IX, and X)

Supplementary information

- **Table S1:** Civilian studies addressing hemorrhagic death
- **Table S2:** Epidemiologic studies of trauma-induced coagulopathy (TIC) since 2000

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