Coagulopathy of Trauma

Mitchell J. Cohen, MD*, S. Ariane Christie, MD

KEYWORDS

• Trauma • Hemorrhage • Coagulation • Coagulopathy
• Trauma-induced coagulopathy • Targeted resuscitation • Bleeding

KEY POINTS

- Trauma-induced coagulopathy (TIC) is an endogenous hypocoagulable state distinct from iatrogenic causes.
- Activation of protein C pathway is a key mechanistic mediator of traumatic coagulopathy via downstream effects, including thrombin diversion, deactivation of coagulation factors, and de-repression of fibrinolysis.
- Standard coagulation tests and functional viscoelastic assays are commonly used in the diagnosis and management of TIC.
- Balanced resuscitation is the mainstay of coagulopathy treatment, but precise ratios for empiric resuscitation and optimal monitoring protocols for transfusion practice remain unknown.
- Patients with traumatic coagulopathy have worse outcomes, including increased rates of transfusion, infection, thromboembolism, acute lung injury, multiorgan failure, and death.

INTRODUCTION

Bleeding remains the leading cause of preventable death after injury.[1] Contributing to this problem, coagulopathy develops in approximately one-third of all injured patients,[2–4] resulting in worsened outcomes including higher transfusion requirements; increased multiorgan system failure, increased hospital, intensive care, and ventilator days; and increased mortality.[2,3,5,6]

Grants: Supported by NIH 1UM1HL10877, DOD W911NF-10-1-0384 (M.J. Cohen).
Conflicts of Interest: None declared.
Department of Surgery, San Francisco General Hospital, University of California, San Francisco, School of Medicine, 1001 Potrero Avenue, San Francisco, CA 94110, USA
* Corresponding author. Department of Surgery, San Francisco General Hospital, Ward 3A, 1001 Potrero Avenue, Room 3C-38, San Francisco, CA 94110.
E-mail address: Mitchell.Cohen@ucsf.edu

Crit Care Clin 33 (2017) 101–118
http://dx.doi.org/10.1016/j.ccc.2016.08.003 **criticalcare.theclinics.com**

History of coagulopathy in trauma

Although coagulopathy was known to occur after injury, until recently coagulation was not viewed as a critical driver of postinjury physiology. Instead, injured patients were thought to be coagulopathic owing only to the iatrogenic secondary effects of hemodilution, hypothermia, and acidosis.[7,8] In 2003, 2 independent investigators described admission perturbations of prothrombin time (PT) and partial thromboplastin time (PTT) in newly injured patients before significant fluid administration.[2,3] This phenomenon, which correlated with increasing injury severity and mortality, became known as "acute traumatic coagulopathy" (now "trauma-induced coagulopathy" [TIC]) and effectively changed the paradigm of modern trauma care.[2,3,9] The study of coagulation and inflammation derangements after injury now constitutes one of the most active areas of ongoing trauma research.

This review addresses the current evidence regarding the diagnosis, mechanisms, and management of TIC, highlighting areas of ongoing debate and controversy. Although TIC is emphasized, it is equally important to recognize that coagulopathy after trauma is often caused or compounded by additional contributors of disordered coagulation including hypothermia, acidosis, dilution with large volume of intravenous fluid, or unbalanced blood product, all of which are termed iatrogenic coagulopathy. Management of the injured coagulopathic patient must therefore include a high suspicion for and treatment of multiple different potential etiologies of dysfunctional clotting.

PATIENT EVALUATION AND OVERVIEW

Mechanism and Pathophysiology

Multiple distinct but highly integrated pathways have been implicated as mediators of TIC (Fig. 1). Delineating the exact pathophysiology and interplay between disordered coagulation and inflammation mechanisms remains the subject of ongoing research. Herein, we describe the most important known contributors to TIC.

Activated protein C and fibrinolysis

TIC is an endogenous hypocoagulable state that occurs in the setting of tissue hypoperfusion (base deficit) and is primarily mediated by activation of protein C (Fig. 2).[10]

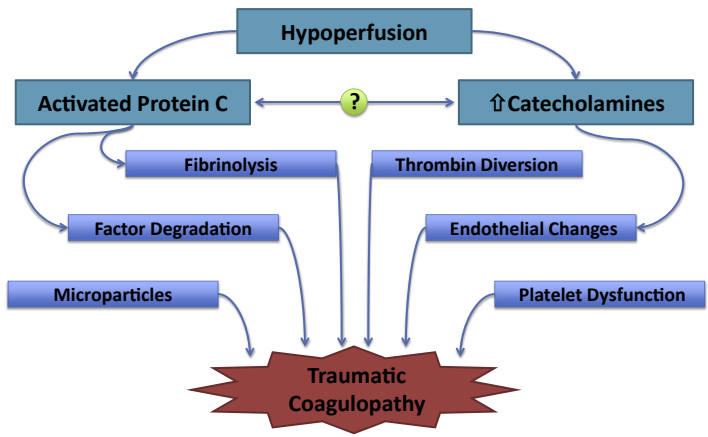

Fig. 1. Pathophysiology of traumatic coagulopathy. Multiple distinct but highly integrated pathways have been implicated as mediators of trauma-induced coagulopathy. Delineation and integration of these pathways remains an area of ongoing research.

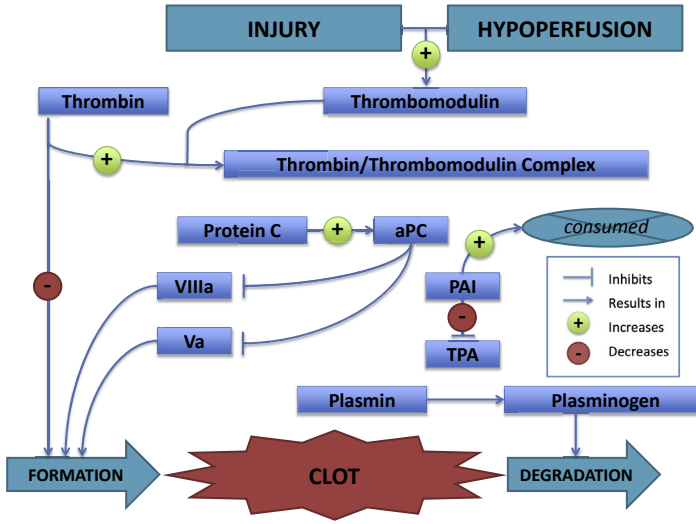

Fig. 2. Critical role of aPC in the pathophysiology of trauma-induced coagulopathy. Severe injury accompanied by tissue hypoperfusion leads to increased endothelial and circulating thrombomodulin, which subsequently binds thrombin. The resultant thrombomodulin-thrombin complex converts protein C into its activated form (aPC). While aPC decreases clot formation via deactivation of factors V and VIII, it is simultaneously consuming plasminogen activator inhibitor-1 (PAI-1), disinhibiting tPA, and leading to unopposed fibrinolysis. APC, activated protein C; PAI, plasminogen activator inhibitor; tPA, tissue plasminogen activator; Va, activated factor V; VIIIa, activated factor VIII.

Multiple prospective clinical studies have linked early coagulopathy in critically injured trauma patients to protein C depletion (activated protein C [aPC] elevation), and increased risk of acute lung injury, ventilator-associated pneumonia, multisystem organ failure, and death.[6,10,11] Protein C is a serine protease with both anticoagulant and inflammomodulatory functions.[12,13] When severe injury is accompanied by shock (tissue hypoperfusion), increased endothelial and circulating thrombomodulin bind thrombin forming thrombomodulin–thrombin complex, which subsequently activates protein C.[10] aPC deactivates factors V and VIII inhibiting clot formation, and depletes plasminogen activator inhibitor-1, leading to unopposed fibrinolysis with increased levels of tissue plasminogen activator and D-dimer.[14]

Fibrinolytic activity is further exacerbated by reduced activation of thrombin-activatable fibrinolysis inhibitor as thrombin is diverted to PC activation.[15] Severe fibrinolysis in TIC portends increased mortality,[16–18] and even low degrees of clot lysis have been associated with poor outcomes.[19] In a murine model, aPC inhibition prevented TIC after trauma and hemorrhagic shock.[12]

Conversely, overinhibition of fibrinolysis, termed "fibrinolysis shutdown," has been demonstrated to be an independent predictor of adverse outcomes after injury, including increased mortality.[20] Furthermore, recent prospective cohort data suggest that more severely injured patients present with fibrinolysis shutdown than either hyperfibrinolysis or physiologic fibrinolysis.[21] These data have important implications with regard to the usefulness of potential fibrinolytic inhibitors, which will need to be carefully targeted to the physiologic range and avoid overinhibition leading to fibrinolysis shutdown.

Platelets

Platelet deficit and dysfunction are also likely to be significant contributors to TIC.[22]

Relative thrombocytopenia Multiple prospective cohort studies have demonstrated that relatively lower admission platelet counts are associated with increased all-cause, hemorrhagic, and central nervous system mortality, and increased blood use after injury, even when the initial platelet count remains well within the normal limits.[23,24] Additionally, the platelet count has been shown to decrease substantially over the course of hospitalization.

Functional platelet impairment Severe injury is also associated with impaired platelet function. In 2001, Jacoby and colleagues[25] used flow cytometery and light aggregrometry first identified decreased admission platelet function in injury nonsurvivors, and, in a separate analysis, in patients with head injury at 24 hours. Thromboelastographic platelet mapping data demonstrated that severely injured trauma patients had impaired platelet stimulation in response to adenosine diphosphate and arachidonic acid stimulation compared with healthy human volunteers, with impairment proportionate to injury severity.[26]

Another prospective clinical study demonstrated that 46% of severely injured patients on admission and 91% of patients at 120 hours had some degree of platelet dysfunction by multiplate impedance aggregometry, despite normal platelet counts.[27] Impaired admission platelet function in response to arachidonic acid, collagen, and thrombin receptor activating peptide were predictive of death. Data from multiple additional animal and clinical studies have corroborated findings of impaired platelet function after severe injury and traumatic brain injury.[28,29]

Endothelial involvement

Recent investigations have also demonstrated evidence that endothelial dysfunction likely plays a role in development of TIC.[30] Admission plasma samples from severely injured patients demonstrate elevated circulating levels of Syndecan-1, a protein normally found in the glycocalyx of the endothelium. Soluble syndecan-1 was associated with increased aPC, prolonged PTT, and increased adrenaline levels, suggesting that tissue hypoperfusion and catecholamine stimulation after injury may result in degradation of the endothelial glycocalyx and contribute to coagulopathy. To date, however, there is no experimental confirmation of this theory, making it possible that the association between catecholamines and coagulopathy is only correlative.

Microparticles

Emerging research suggests that microparticles may also play a role in the mechanism of TIC. Some evidence suggests that systemic release of thrombin-rich microparticles, which likely function normally in local hemostasis after tissue injury, may cause a coagulopathic state similar to DIC. Elevated circulating endothelial-, erythrocyte-, and leukocyte-derived microparticles have been identified in the plasma of injured patients compared with noninjured controls whereas coagulopathic patients demonstrated lower levels of platelet-derived and tissue factor–positive microparticles compared with noncoagulopathic patients.[31] In a single small study, increased circulating microparticles were also found in patients with traumatic brain injury compared with controls.[32]

Diagnosis

Standard clinical and laboratory assessment after severe injury

As with the management of all severely injured patients, diagnosis of TIC should be performed within the context of the Advanced Trauma Life Support evaluation. Obvious sources of active bleeding should be temporized promptly with compression or other hemostatic measures,

hypotension should be addressed with administration of packed red blood cells (PRBC), and the patient should be warmed with heated blankets as the patient is exposed. Severe injury and hypotension should prompt a high degree of suspicion for traumatic coagulopathy. Standard trauma laboratory tests should be obtained as soon as intravenous access is secured and can provide indicators of the presence of tissue hypoperfusion and coagulopathy. Table 1 describes standard admission trauma laboratory tests and their role in the diagnosis of TIC.

Table 1
Standard admission trauma laboratory measures in the evaluation of TIC

Lab	Level	Usefulness in the Diagnosis of TIC
pH	Low	Significant hypoperfusion probable
Base deficit/excess	Negative	Significant hypoperfusion probable
Hemoglobin/hematocrit	Low	Likely significant blood loss
Platelet count	Low	Absolute/relative thrombocytopenia
Partial thromboplastin time	Prolonged	Diagnostic of TIC
Prothrombin time/International Normalized Ratio	Prolonged	Diagnostic of TIC

Abbreviation: TIC, trauma-induced coagulopathy.

We also recommend the standard collection of baseline fibrinogen and D-dimer, which can provide a surrogate estimation of factor consumption and fibrinolysis, respectively.

Diagnostic criteria

Multiple assays currently play a role in the diagnosis of TIC.

Standard assays TIC was initially defined by prolongation of the standard coagulation assays PTT and PT/International Normalized Ratio (INR), and these remain the most widely used method for the diagnosis of TIC. Different cutoffs for these assays have been described in the literature (Table 2).

Macleod and colleagues[3] reported that alterations in the cutoffs for PTT and PT did not alter the predictive value of these variables for predicting death in an adjusted regression model. Lower thresholds for INR cutoffs demonstrated improved sensitivity to discriminate patients with higher transfusion requirements in shock in severely injured population (Injury Severity Score >15) in a multicenter retrospective study, but at least 1 prospective study has refuted this finding.[36]

However, concerns have been raised regarding the use of standard coagulation assays as the benchmark for TIC. PTT and INR were designed initially to test heritable coagulopathy, and standard reference ranges were generated using data from healthy volunteers. Additionally, concerns have been raised regarding the length of time required to run standard coagulation tests when rapid and ongoing diagnosis and treatment of the coagulopathic patient are essential to reverse pathophysiology and improve outcomes.

Table 2
Commonly used cutoffs for conventional coagulation assays in trauma-induced coagulopathy

Assay	Cutoff	Or	Any value >1.5× the institutional reference range[33]
Partial thromboplastin time	>34–60 sec[3,30]		
Prothrombin time	>18 sec		
International Normalized Ratio	>1.2–1.5[3,6,34,35]		

Viscoelastic assays There has been increased interest and use of point-of-care functional tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for the diagnosis and management of patients with TIC. TEG is a modality that assesses multiple real-time viscoelastic properties of coagulation including:

- Time to clot initiation,
- Clot propagation,
- Clot strength, and
- Clot breakdown (fibrinolysis).

The addition of specific clotting activators and inhibitors can be used to assay different contributors to clot formation or breakdown. Multiple studies have demonstrated the capacity of TEG to diagnose hypocoagulability and predict transfusion and mortality in the trauma population.[37–40] TEG has been validated against standard coagulation tests,[40] and assays of both thrombin generation[41] and fibrinolysis.[42] However, there remains ongoing debate regarding the superiority of TEG compared with other assays, in particular with regards to fibrinolysis as plasmin–antiplasmin levels have demonstrated high sensitivity.[43]

Scoring systems Multiple scoring systems have been generated to predict need for massive transfusion, including:

- The Trauma-Associated Severe Hemorrhage score,[44]
- The McLaughlin score,[45] and
- The Assessment of Blood Consumption score.[46]

A retrospective review comparing these 3 scoring systems failed to demonstrate a difference between their capacity to predict massive transfusion.[46] Importantly, the scoring systems do not take into account coagulation parameters and likely reflect significant hemorrhage owing to injury rather than TIC proper. None of these scoring systems have been used widely in the diagnosis of TIC.

Phenotypes of Trauma-Induced Coagulopathy

There is evidence to suggest that traumatic coagulopathy is not a single entity, but rather consists of multiple distinct but related pathophysiologic subtypes. A principle component analysis of a large prospective cohort of injured patients demonstrated 2 such phenotypes.

1. **Coagulation factor deficiency TIC**
   a. Characterized by abnormality of standard coagulation tests and increased mortality.
2. **Fibrinolytic TIC**
   a. Characterized by aPC elevation and is associated with increased end organ failure, infectious complications and mortality.[9]

There are likely even more TIC subtypes that have yet to be identified. By diagnosing and treating specific deficits underlying different coagulopathic phenotypes, it may be possible to streamline individualized care and improved outcomes.

PHARMACOLOGIC TREATMENT OPTIONS

Although balanced product transfusion currently remains the mainstay of treatment for TIC, there are several pharmacologic agents that have the potential to be efficacious based on our mechanistic understanding of traumatic coagulopathy.

Antifibrinolytics

Evidence of hyperfibrinolysis as a critical mechanism underlying traumatic coagulopathy has led to interest antifibrinolytic agents as potential adjuncts for the treatment of TIC. These agents include tranexamic acid (TXA), aminocaproic acid, and aprotinin, of which only TXA has been widely studied in trauma patients.

The CRASH-2 trial (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) was a large international randomized trial that reported a 1.5% absolute mortality reduction in patients administered TXA compared with placebo, although there was no difference in blood product transfusion between groups. Furthermore, the subset of patients who received TXA 3 or more hours after injury had increased mortality.[47] Of note, enrollment criteria for this study failed to incorporate coagulation data and included any patients with or at risk for significant hemorrhage limiting the generalizability of these findings.

The MATTERs (Military Application of Tranexamic-acid in Trauma Emergency Resuscitation) study was a retrospective observational study, which identified reduced mortality in patients who received TXA, with greater differences identified in patients requiring massive transfusion.[48] Despite achieving considerable acceptance as an adjunctive treatment for TIC, there has not yet been sufficient evidence to support the routine use of TXA in the trauma setting.[49]

Recombinant Factor Concentrates

Additional pharmaceutical hemostatic agents with potential usefulness in the treatment of TIC include recombinant factor concentrates including recombinant factor VIIa, prothrombin complex concentrate (PCC), and fibrinogen.

Recombinant Factor VII

Fresh frozen plasma (FFP) is often used to reverse coagulopathy, but has limitations including the requirement for thawing and cross-matching, incomplete and variable factor level repletion,[50–52] and coagulation test reversal[53,54] and complications such as transfusion-related acute lung injury and circulatory overload.[55,56]

Physiologically targeted resuscitation could theoretically arrest coagulopathy in a rapid fashion and avoid many of the pitfalls of traditional plasma. There was significant interest in using recombinant factor VIIa to do this; however, key trials failed to show benefit and suggested increased thrombotic complications.[57] It has been pointed out that these trials generally used recombinant factor VIIa late in the resuscitation process, when poor outcomes were relatively certain. It is not known whether recombinant factor VIIa could potentially have a role in trauma resuscitation as part of a more targeted empiric therapy for specific subpopulations of patients with TIC, but at present factor VIIa has not gained widespread support for use in the trauma setting.

Prothrombin Complex Concentrate

PCC comes in several varieties, including 3- and 4-factor formulations. The most common formulation is 4-factor PPC, a human plasma–derived concentrate of vitamin K–dependent clotting factors II, VII, IX, and X that received approval from the US Food and Drug Administration in April 2013 as an alternative to urgent warfarin reversal in the setting of acute bleeding or need for urgent surgery. Since that time, it has developed usage for reversal of nonwarfarin coagulopathy, including coagulopathy induced by new oral anticoagulants and in coagulopathy of nonmedication etiologies.[58–60]

In a porcine trauma models, PCC demonstrated more rapid and effective hemostasis than FFP in the correction of acquired coagulopathy.[61] Multiple retrospective

studies have reported decreased time to reversal, decreased product use, and decreased mortality in patients treated with PCC in the setting of traumatic coagulopathy in general and in the population with traumatic brain injury.[62,63] However, there are ongoing concerns regarding the potential for increased thromboembolic complications and cost with 4-factor PPC compared with plasma. At present, the paucity of prospective data limits our ability to draw conclusions regarding the safety and efficacy of 4-factor PPC in severe injury.

Fibrinogen Concentrate

Fibrinogen deficit has been shown to predict TIC,[11] and as described fibrinolysis constitutes an important component of the pathophysiology of TIC. In a prospective cohort study of 517 trauma patients, low fibrinogen levels were independent predictor of mortality at 24 hours and 28 days ($P<.001$), and administration of cryoprecipitate was associated with improved survival.[64] Although the threshold of sufficient fibrinogen to support normal clotting has not been studied rigorously in trauma patients, routine testing and repletion of low admission levels or function may be a reasonable adjunct to the treatment of TIC. FFP does not contain sufficient amounts of fibrinogen for adequate replacement[65] and in the United States cryoprecipitate is commonly used for this purpose. In Europe, retrospective studies in a trauma population have reported good efficacy of fibrinogen concentrate in correcting functional deficits,[66] however, this product is not currently approved in the United States. Current European guidelines for hemorrhage management in trauma patients with fibrinogen levels less than 1.5 to 2.0 g/L or viscoelastic signs of a functional fibrinogen deficit recommend an initial fibrinogen concentrate dose of 3 to 4 g (equivalent to 15–20 single donor units of cryoprecipitate), with further dosing guided by laboratory or viscoelastic testing (**Fig. 3**).[67]

NONPHARMACOLOGIC TREATMENT OPTIONS

Treatment of coagulopathy in the injured patient includes early diagnosis, prompt hemostasis, and early hemorrhage control, prevention of complicating causes of coagulopathy (hypothermia, acidosis, hemodilution), and blood product transfusion with FFP, platelets, and cryoprecipitate. There is ongoing debate regarding the optimal protocol for delivery of blood product resuscitation.

Balanced Resuscitation and Resuscitation Ratios

Although early transfusion was conducted with whole blood, in the last quarter of the 21st century standard practice favored resuscitation of the injured patient with large volumes of crystalloid and PRBC.[68] Then, in the early 2000s, retrospective military data from Afghanistan and Iraq suggested a mortality benefit to trauma resuscitation with a balanced ratio of PRBCs.[69] Civilian retrospective data echoed these findings using a 1:1:1 ratio of PRBCs, FFP, and platelets[70,71] and the trauma community subsequently began to shift toward balanced blood product resuscitation (**Fig. 4**).

The PROMMTT study (Prospective, Observational, Multicenter, Major Trauma Transfusion) demonstrated in a large multicenter cohort that patients who received increased plasma to RBC ratios had reduced 6-hour mortality compared with those who received less plasma.[72] In an attempt to delineate the ideal empiric transfusion ratio, the (PROPPR) trial (Pragmatic, Randomized Optimal Platelet and Plasma Ratios) randomized severely injured patients to 1:1:1 versus 1:1:2 PRBC to FFP to platelet resuscitation, but ultimately failed to demonstrate a difference between resuscitation groups for 24-hour or 28-day mortality,[73] which was likely at least in part owing to poor separation between treatment groups. At present, the precise “ideal” PRBC to plasma

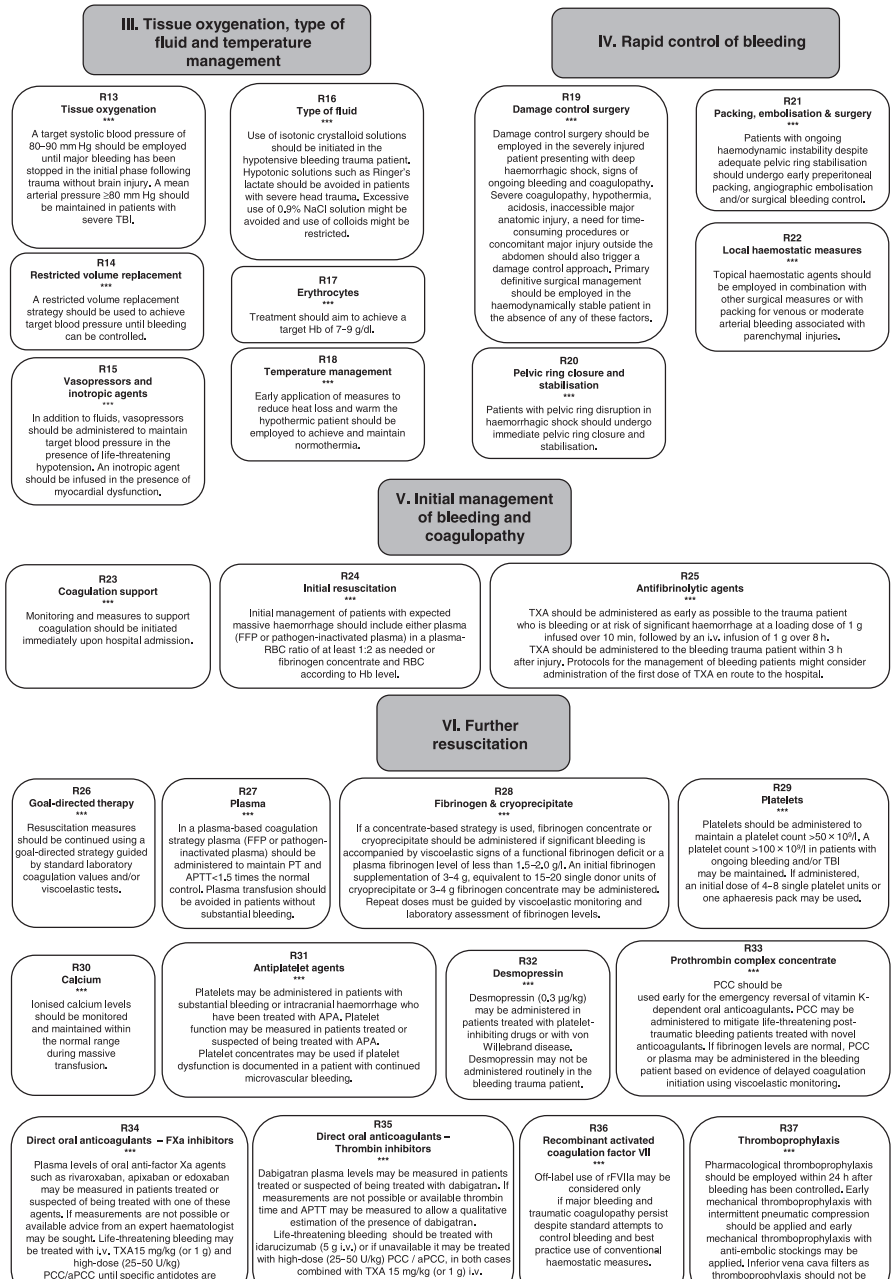

Fig. 3. Recommendations of European Guideline on management of major bleeding and coagulopathy after trauma, 2016. APA, antiplatelet agents; aPCC, activated prothrombin complex concentrate; APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; Hb, hemoglobin; PCC, prothrombin complex concentrate; PT, prothrombin time; RBC, red blood cells; rFVIIa, recombinant factor VIIa; TBI, traumatic brain injury; TXA, tranexamic acid. (*Adapted from* Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100.)

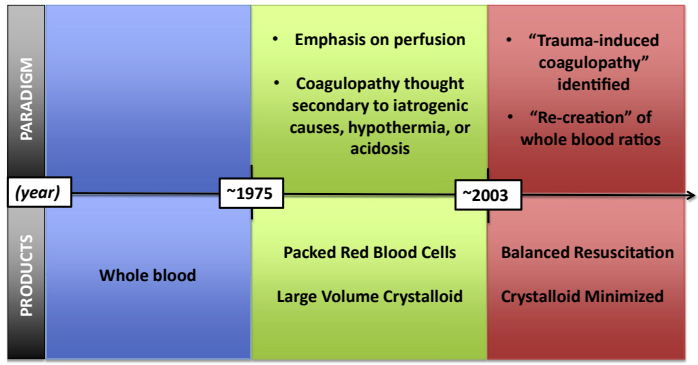

Fig. 4. Evolution of paradigms and resuscitation of injured patients over time. Early transfusion was conducted with whole blood. In the 1970s, resuscitation practice shifted toward an emphasis on perfusion with heavy use of large volumes of crystalloid and packed red blood cells (PRBC). Coagulopathy was understood to occur in severely injured patients but was not recognized as a distinct entity. Rather, it was attributed to iatrogenic dilution, hypothermia, or acidosis. In 2003, trauma-induced coagulopathy was identified as a distinct entity and treatment shifted away from crystalloid and toward balanced hemostatic resuscitation.

to platelet ratio remains undetermined; however, it remains clear that limitation of crystalloid and balanced product transfusion approximating whole blood improve outcomes and should be priorities of trauma resuscitation.

COMBINATION THERAPIES

Targeted Resuscitation Practice

A different paradigm for treatment of the patient with TIC proposes a targeted approach to resuscitation. In this approach, laboratory assays, including point-of-care TEG, are obtained in a serial fashion and used to guide product transfusion and administration of pharmaceutical adjuncts. This allows resuscitation to be tailored to the individual patient in real time, and coordinates the different modalities available for treatment. An additional advantage to this approach is the ability to provide dynamic management as the patient's condition changes. Objections to this approach include the need for infrastructure to support serial and rapid TEG assays, and that these tests depend on and vary by user skill and interpretation.

A recent Cochrane review suggested that there was insufficient evidence to recommend TEG-based transfusion guidelines as superior to established transfusion practice.[74] However, recently published prospective randomized data from the Denver group shows a mortality benefit when viscoelastic functional testing (TEG) was used to guide massive transfusion protocols compared with conventional coagulation assays (CCA).[75] Survival in the TEG group was significantly higher than the CCA group (28-day mortality 36.4% CCA vs 19.6% TEG) and 6-hour mortality was significantly lower in the TEG group (21.7% CCA vs 7.1% TEG; $P = .032$). Importantly, not all centers have access to TEG, and these centers should perform frequent serial measurements of PT/INR, PTT, platelets, hemoglobin/hematocrit, fibrinogen, and D-dimer to help guide resuscitation practice.

SURGICAL TREATMENT OPTIONS

Surgical management of trauma coagulopathy should be directed toward prompt cessation of any anatomic causes of hemorrhage, and thereby avoidance of

what has been termed the "lethal triad" of coagulopathy, hypothermia, and acidosis.

TREATMENT RESISTANCE AND COMPLICATIONS

Compounding Coagulopathy

If prompt diagnosis and tailored resuscitation fails to improve TIC, compounding etiologies of coagulopathy should be strongly suspected. These can include hypothermia, acidosis, hemodilution, DIC, and heritable coagulopathies. Treatment includes the approaches described, as well as the following considerations.

Hypothermia

Hypothermia (temperature <36°C) is present in approximately two-thirds of injured patients on admission, and 9% of patients present with severe hypothermia (temperature <33°C) owing to a combination of exposure in the field and during transport and administration of cold intravenous fluids.[76] Patients are at further risk for worsening of hypothermia in the emergency room and operating room, if necessary. Mild to moderate hypothermia (temperature 33°C–36°C) results in impaired platelet aggregation and adhesion and decreased tissue factor activity leading to coagulopathy that is typically not detectable using standard or functional coagulations assays as samples are routinely warmed before testing.[77] Therefore, it is essential to maintain a high level of vigilance against hypothermia with continuous temperature monitoring. All trauma patients should receive passive rewarming with removal of clothing and application warmed blankets, as well as warming of administered fluids. Central warming should be considered in cases of severe or resistant hypothermia.

Acidosis

Severely injured patients frequently present with or develop acidosis during the course of their resuscitation. Assembly of functional coagulation factor complexes are inhibited in acidotic environments (pH <7.2) with increasing dysfunction as acidosis worsens.[78,79] Arterial blood gas should be obtained at admission and repeated at serial time points throughout resuscitation with correction of acidosis as necessary.

Hemodilution

Dilutional coagulopathy, also known as "iatrogenic" or "resuscitation–associated coagulopathy" occurs when coagulation factor proteins are diluted by large volumes of crystalloid, colloid, or PRBCs. Coagulation factor dilution with large volume administration has been demonstrated in multiple laboratory, modeling and healthy control studies.[80–82] Retrospective data have shown admission coagulopathy to be significantly more prevalent among injured patients who received more than 3 L of prehospital fluids compared with those who received little (<500 mL) or no volume.[4] To avoid dilutional coagulopathy, resuscitation should consist primarily of balanced product transfusion with frequent monitoring of ongoing coagulation status. Crystalloid should no longer be considered a resuscitation fluid and only used to facilitate administration of medications and blood products.

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) occurs as a result of systemic microvascular thrombosis causing severe consumptive coagulopathy. Although now understood to be a distinct pathology, some features of DIC overlap with traumatic coagulopathy, making diagnosis challenging. Trauma patient are at increased risk for DIC owing to the potential for embolization of tissue-specific thromboplastin after long bone fractures, amniotic disruption, or brain injury, or later in the clinical course as

a result of sepsis. DIC should be considered as an alternate or concomitant etiology of late, recurrent, or treatment-resistant coagulopathy in the severely injured patient, but is not a cause of acute traumatic coagulopathy.

EVALUATION OF OUTCOME AND LONG-TERM RECOMMENDATIONS

Outcomes after treatment of TIC should be assessed by:

1. Improvement in the clinical condition of the injured patient including a trend toward global hemostasis and hemodynamic stability and
2. Reversal of standard and functional laboratory coagulation abnormalities.

Despite advances in the understanding, diagnosis, and resuscitation of injured patients with TIC, patients with traumatic coagulopathy go on to have worse outcomes than noncoagulopathic patients.

Transfusion Requirements

Compared with noncoagulopathic patients, patients with TIC receive substantially increased blood product transfusion,[10] which independently confers a greater risk of complications such as acute respiratory distress syndrome,[83] systemic inflammatory response syndrome,[84] and mortality after injury.[85] As noted, there is no consensus regarding ideal ratios of resuscitation; however, ongoing observational experience from institutions with massive transfusion protocols have described decreased crystalloid and overall product use, and lower PRBC:FFP ratios with concomitant survival benefit.[86]

Hypercoagulability

Multiple investigators have reported an increased incidence of thromboembolic complications in patients with early TIC.[36,87] Given the potential risks of anticoagulation in this patient population, multiple scoring systems including the Trauma Embolic Scoring System and the Risk Assessment Profile have attempted to stratify patients at high risk for venous thromboembolism (VTE), but recent retrospective data suggest that scoring systems often fail to discriminate between patients who go on to develop VTE.[88] It also remains unclear whether standard or functional assays can accurately predict clinically significant hypercoagulability in critically ill trauma patients.[89] Many studies investigating VTE in trauma patients relay on duplex screening, and the significance of these incidentally discovered events remains unknown. Finally, there has not been sufficient evidence to definitively establish whether standard chemoprophylaxis is efficacious in mitigating thromboembolic risk in this population.[90] Further prospective clinical studies are necessary to better delineate the mechanism of VTE in previously coagulopathic trauma patients and to identify potential targets for prevention and treatment.

Acute Lung Injury, Multiorgan Failure, and Death

Despite substantive progress in delineation of the mechanism of TIC and improved outcomes resulting from changes in resuscitation practice, patients with traumatic coagulopathy have vastly increased rates of acute lung injury, multiorgan failure, and death. Unsurprisingly, these patients also have worse hospital metrics, including more days spent on the ventilator, in the intensive care unit, and in the hospital than do noncoagulopathic patients. This highlights the need for continued research efforts and clinical innovation to combat this considerable clinical challenge and improve outcomes. One potential approach is through focus on individualization of diagnosis

and resuscitation. As discussed, there is evidence to suggest that traumatic coagulopathy is not a single entity, but rather consists of multiple phenotypes with unique implications for outcomes and management.

SUMMARY

- TIC is an endogenous hypocoagulable state distinct from iatrogenic, dilution, or hypothermic causes.
- Activation of the protein C pathway is a key mechanistic mediator of TIC via multiple downstream effects including thrombin diversion, deactivation of coagulation factors, and de-repression of fibrinolysis.
- Standard coagulation tests and functional viscoelastic assays are commonly used in the diagnosis and management of TIC.
- Balanced resuscitation is the mainstay of TIC treatment, but precise ratios for empiric resuscitation and optimal monitoring protocols for transfusion practice remain hotly debated.
- Patients with TIC have worse outcomes including increased rates of transfusion, infection, thromboembolism, acute lung injury, multiorgan failure, and death.

REFERENCES

1. Sauaia A, Moore FA, Moore EE, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38(2):185–93.
2. Brohi K, Singh J, Heron M, et al. Acute traumatic coagulopathy. J Trauma 2003; 54(6):1127–30.
3. MacLeod JB, Lynn M, McKenney MG, et al. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55(1):39–44.
4. Maegele M, Lefering R, Yucel N, et al. Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007;38(3): 298–304.
5. Cohen MJ, Bir N, Rahn P, et al. Protein C depletion early after trauma increases the risk of ventilator-associated pneumonia. J Trauma 2009;67(6):1176–81.
6. Cohen MJ, Call M, Nelson M, et al. Critical role of activated protein C in early coagulopathy and later organ failure, infection and death in trauma patients. Ann Surg 2012;255(2):379–85.
7. Hess JR, Brohi K, Dutton RP, et al. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008;65(4):748–54.
8. Kirkpatrick AW, Chun R, Brown R, et al. Hypothermia and the trauma patient. Can J Surg 1999;42(5):333–43.
9. Kutcher ME, Ferguson AR, Cohen MJ. A principal component analysis of coagulation after trauma. J Trauma Acute Care Surg 2013;74(5):1223–9 [discussion: 1229–30].
10. Brohi K, Cohen MJ, Ganter MT, et al. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007; 245(5):812–8.
11. Cohen MJ, Kutcher M, Redick B, et al. Clinical and mechanistic drivers of acute traumatic coagulopathy. J Trauma Acute Care Surg 2013;75(1 Suppl 1):S40–7.
12. Chesebro BB, Rahn P, Carles M, et al. Increase in activated protein C mediates acute traumatic coagulopathy in mice. Shock 2009;32(6):659–65.
13. Esmon CT. Protein C pathway in sepsis. Ann Med 2002;34(7–8):598–605.

14. Rezaie AR. Vitronectin functions as a cofactor for rapid inhibition of activated protein C by plasminogen activator inhibitor-1. Implications for the mechanism of profibrinolytic action of activated protein C. J Biol Chem 2001;276(19):15567–70.
15. Bajzar L, Jain N, Wang P, et al. Thrombin activatable fibrinolysis inhibitor: not just an inhibitor of fibrinolysis. Crit Care Med 2004;32(5 Suppl):S320–4.
16. Schochl H, Frietsch T, Pavelka M, et al. Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 2009;67(1):125–31.
17. Kashuk JL, Moore EE, Sawyer M, et al. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg 2010;252(3):434–42 [discussion: 443–4].
18. Cotton BA, Harvin JA, Kostousouv V, et al. Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration. J Trauma Acute Care Surg 2012;73(2):365–70 [discussion: 370].
19. Chapman MP, Moore EE, Ramos CR, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. J Trauma Acute Care Surg 2013; 75(6):961–7 [discussion: 967].
20. Moore HB, Moore EE, Gonzalez E, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg 2014;77(6):811–7 [discussion: 817].
21. Moore HB, Moore EE, Liras IN, et al. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. J Am Coll Surg 2016;222(4):347–55.
22. Davenport RA, Brohi K. Coagulopathy in trauma patients: importance of thrombocyte function? Curr Opin Anaesthesiol 2009;22(2):261–6.
23. Brown LM, Call MS, Margaret Knudson M, et al. A normal platelet count may not be enough: the impact of admission platelet count on mortality and transfusion in severely injured trauma patients. J Trauma 2011;71(2 Suppl 3):S337–42.
24. Stansbury LG, Hess AS, Thompson K, et al. The clinical significance of platelet counts in the first 24 hours after severe injury. Transfusion 2013;53(4):783–9.
25. Jacoby RC, Owings JT, Holmes J, et al. Platelet activation and function after trauma. J Trauma 2001;51(4):639–47.
26. Wohlauer MV, Moore EE, Thomas S, et al. Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. J Am Coll Surg 2012;214(5): 739–46.
27. Kutcher ME, Redick BJ, McCreery RC, et al. Characterization of platelet dysfunction after trauma. J Trauma Acute Care Surg 2012;73(1):13–9.
28. Sillesen M, Johansson PI, Rasmussen LS, et al. Platelet activation and dysfunction in a large-animal model of traumatic brain injury and hemorrhage. J Trauma Acute Care Surg 2013;74(5):1252–9.
29. Solomon C, Traintinger S, Ziegler B, et al. Platelet function following trauma. A multiple electrode aggregometry study. Thromb Haemost 2011;106(2):322–30.
30. Johansson PI, Stensballe J, Rasmussen LS, et al. A high admission syndecan-1 level, a marker of endothelial glycocalyx degradation, is associated with inflammation, protein C depletion, fibrinolysis, and increased mortality in trauma patients. Ann Surg 2011;254(2):194–200.
31. Matijevic N, Wang YW, Wade CE, et al. Cellular microparticle and thrombogram phenotypes in the Prospective Observational Multicenter Major Trauma Transfusion (PROMMTT) study: correlation with coagulopathy. Thromb Res 2014; 134(3):652–8.

32. Nekludov M, Mobarrez F, Gryth D, et al. Formation of microparticles in the injured brain of patients with severe isolated traumatic brain injury. J Neurotrauma 2014; 31(23):1927–33.
33. Hoyt DB, Dutton RP, Hauser CJ, et al. Management of coagulopathy in the patients with multiple injuries: results from an international survey of clinical practice. J Trauma 2008;65(4):755–64 [discussion: 764–5].
34. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 2007;13(6):680–5.
35. Kashuk JL, Moore EE, Johnson JL, et al. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma 2008; 65(2):261–70 [discussion: 270–1].
36. Peltan ID, Vande Vusse LK, Maier RV, et al. An International normalized ratio-based definition of acute traumatic coagulopathy is associated with mortality, venous thromboembolism, and multiple organ failure after injury. Crit Care Med 2015;43(7):1429–38.
37. Kaufmann CR, Dwyer KM, Crews JD, et al. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 1997;42(4):716–20 [discussion: 720–2].
38. Carroll RC, Craft RM, Langdon RJ, et al. Early evaluation of acute traumatic coagulopathy by thrombelastography. Transl Res 2009;154(1):34–9.
39. Rugeri L, Levrat A, David JS, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Thromb Haemost 2007;5(2): 289–95.
40. Cotton BA, Faz G, Hatch QM, et al. Rapid thrombelastography delivers real-time results that predict transfusion within 1 hour of admission. J Trauma 2011;71(2): 407–14 [discussion: 414–7].
41. Rivard GE, Brummel-Ziedins KE, Mann KG, et al. Evaluation of the profile of thrombin generation during the process of whole blood clotting as assessed by thrombelastography. J Thromb Haemost 2005;3(9):2039–43.
42. Levrat A, Gros A, Rugeri L, et al. Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth 2008;100(6): 792–7.
43. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost 2013;11(2):307–14.
44. Yucel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma 2006;60(6):1228–36 [discussion: 1236–7].
45. McLaughlin DF, Niles SE, Salinas J, et al. A predictive model for massive transfusion in combat casualty patients. J Trauma 2008;64(2 Suppl):S57–63 [discussion: S63].
46. Nunez TC, Voskresensky IV, Dossett LA, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma 2009;66(2):346–52.
47. CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376(9734):23–32.
48. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg 2012; 147(2):113–9.

49. Napolitano LM, Cohen MJ, Cotton BA, et al. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg 2013;74(6):1575–86.
50. Chowdary P, Saayman AG, Paulus U, et al. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004;125(1):69–73.
51. Cardigan R, Lawrie AS, Mackie IJ, et al. The quality of fresh-frozen plasma produced from whole blood stored at 4 degrees C overnight. Transfusion 2005;45(8):1342–8.
52. Stanworth SJ. The evidence-based use of FFP and cryoprecipitate for abnormalities of coagulation tests and clinical coagulopathy. Hematology Am Soc Hematol Educ Program 2007;179–86.
53. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion 2006;46(8):1279–85.
54. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion: the effect of plasma transfusion on coagulation test results. Am J Clin Pathol 2006;126(1):133–9.
55. Kor DJ, Stubbs JR, Gajic O. Perioperative coagulation management–fresh frozen plasma. Best Pract Res Clin Anaesthesiol 2010;24(1):51–64.
56. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood 2012;119(7):1757–67.
57. Levi M, Levy JH, Andersen HF, et al. Safety of recombinant activated factor VII in randomized clinical trials. N Engl J Med 2010;363(19):1791–800.
58. Marlu R, Hodaj E, Paris A, et al. Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost 2012;108(2):217–24.
59. Gorlinger K, Dirkmann D, Hanke AA, et al. First-line therapy with coagulation factor concentrates combined with point-of-care coagulation testing is associated with decreased allogeneic blood transfusion in cardiovascular surgery: a retrospective, single-center cohort study. Anesthesiology 2011;115(6):1179–91.
60. Tanaka KA, Mazzeffi M, Durila M. Role of prothrombin complex concentrate in perioperative coagulation therapy. J Intensive Care 2014;2(1):60.
61. Dickneite G, Pragst I. Prothrombin complex concentrate vs fresh frozen plasma for reversal of dilutional coagulopathy in a porcine trauma model. Br J Anaesth 2009;102(3):345–54.
62. Schochl H, Nienaber U, Hofer G, et al. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010;14(2):R55.
63. Joseph B, Pandit V, Khalil M, et al. Use of prothrombin complex concentrate as an adjunct to fresh frozen plasma shortens time to craniotomy in traumatic brain injury patients. Neurosurgery 2015;76(5):601–7 [discussion: 607].
64. Rourke C, Curry N, Khan S, et al. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. J Thromb Haemost 2012;10:1342–51.
65. Theusinger OM, Baulig W, Seifert B, et al. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth 2011;106(4):505–11.
66. Schlimp CJ, Voelckel W, Inaba K, et al. Impact of fibrinogen concentrate alone or with prothrombin complex concentrate (+/- fresh frozen plasma) on plasma

fibrinogen level and fibrin-based clot strength (FIBTEM) in major trauma: a retrospective study. Scand J Trauma Resusc Emerg Med 2013;21:74.
67. Rossaint R, Bouillon B, Cerny V, et al. The European Guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care 2016;20:100.
68. Duchesne JC, Kimonis K, Marr AB, et al. Damage control resuscitation in combination with damage control laparotomy: a survival advantage. J Trauma 2010; 69(1):46–52.
69. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007;63(4):805–13.
70. de Biasi AR, Stansbury LG, Dutton RP, et al. Blood product use in trauma resuscitation: plasma deficit versus plasma ratio as predictors of mortality in trauma (CME). Transfusion 2011;51(9):1925–32.
71. Brown LM, Aro SO, Cohen MJ, et al. A high fresh frozen plasma: packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. J Trauma 2011; 71(2 Suppl 3):S358–63.
72. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013;148(2): 127–36.
73. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA 2015;313(5):471–82.
74. Hunt H, Stanworth S, Curry N, et al. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma induced coagulopathy in adult trauma patients with bleeding. Cochrane Database Syst Rev 2015;(2):CD010438.
75. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed hemostatic resuscitation of trauma-induced coagulopathy: a pragmatic randomized clinical trial comparing a viscoelastic assay to conventional coagulation assays. Ann Surg 2016;263(6): 1051–9.
76. Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. Injury 2004;35(1):7–15.
77. Wolberg AS, Meng ZH, Monroe DM 3rd, et al. A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 2004;56(6):1221–8.
78. Martini WZ. Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. J Trauma 2009;67(1):202–8 [discussion: 208–9].
79. Engstrom M, Schott U, Romner B, et al. Acidosis impairs the coagulation: a thromboelastographic study. J Trauma 2006;61(3):624–8.
80. Hirshberg A, Dugas M, Banez EI, et al. Minimizing dilutional coagulopathy in exsanguinating hemorrhage: a computer simulation. J Trauma 2003;54(3):454–63.
81. Coats TJ, Brazil E, Heron M. The effects of commonly used resuscitation fluids on whole blood coagulation. Emerg Med J 2006;23(7):546–9.
82. Brazil EV, Coats TJ. Sonoclot coagulation analysis of in-vitro haemodilution with resuscitation solutions. J R Soc Med 2000;93(10):507–10.
83. Silverboard H, Aisiku I, Martin GS, et al. The role of acute blood transfusion in the development of acute respiratory distress syndrome in patients with severe trauma. J Trauma 2005;59(3):717–23.

84. Dunne JR, Malone DL, Tracy JK, et al. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt) 2004;5(4):395–404.
85. Charles A, Shaikh AA, Walters M, et al. Blood transfusion is an independent predictor of mortality after blunt trauma. Am Surg 2007;73(1):1–5.
86. Kutcher ME, Kornblith LZ, Narayan R, et al. A paradigm shift in trauma resuscitation: evaluation of evolving massive transfusion practices. JAMA Surg 2013; 148(9):834–40.
87. Knudson MM, Collins JA, Goodman SB, et al. Thromboembolism following multiple trauma. J Trauma 1992;32(1):2–11.
88. Zander AL, Van Gent JM, Olson EJ, et al. Venous thromboembolic risk assessment models should not solely guide prophylaxis and surveillance in trauma patients. J Trauma Acute Care Surg 2015;79(2):194–8.
89. Van Haren RM, Valle EJ, Thorson CM, et al. Hypercoagulability and other risk factors in trauma intensive care unit patients with venous thromboembolism. J Trauma Acute Care Surg 2014;76(2):443–9.
90. Allen CJ, Murray CR, Meizoso JP, et al. Coagulation profile changes due to thromboprophylaxis and platelets in trauma patients at high-risk for venous thromboembolism. Am Surg 2015;81(7):663–8.