Trauma-related Coagulopathy—Current Concepts

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Abstract

Background: Hemorrhage continues to be a major cause of early death in trauma patients. Our understanding of the development of coagulopathy and its importance has evolved significantly over the last decade. In this article, we describe the current understanding of coagulopathy in the setting of trauma including its mechanisms, diagnosis, consequences, and treatment strategies.

Methods: Review of selected articles from MEDLINE.

Results: The occurrence of coagulopathy is common in trauma patients and is multifactorial, with increasing evidence indicating an endogenous mechanism unrelated to the complications of medical treatment. The use of novel coagulation assessment techniques and evolution in blood product treatment strategies is generating a new era of targeted management.

Conclusions: Coagulopathy in trauma is common, but newer techniques in diagnosis as well as novel methods to provide targeted treatment offer encouraging results in decreasing the mortality rate from exsanguination after injury.

Keywords

Trauma, coagulopathy, resuscitation, TEG, ROTEM, damage control resuscitation

Disclosure: The authors have no conflicts of interest to disclose.

Received: May 14, 2012 **Accepted:** September 11, 2012 **Citation:** *Oncology & Hematology Review*, 2012;8(2):123–8 *DOI: 10.17925/OHR.2012.08.2.123*

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Tissue trauma induces alterations in the inflammatory and coagulation systems; in fact, the absence of such responses would almost certainly have resulted in our demise long ago. Along with our protective evolutionary devices, we have also increased our understanding of the coagulopathy induced by trauma over the last few decades—including its distinctive yet parallel interplay with iatrogenic-induced coagulopathy.

Hemorrhage is recognized as the second leading cause of death in trauma patients overall and the leading cause of death during the first few hours of hospital care.[1] Coagulopathic bleeding in the setting of major trauma was recognized over 30 years ago, with the description of the vicious cycle of bleeding, tissue hypoxia, hypothermia, acidosis, and coagulopathy[2] (see *Figure 1*). In 2003, seminal studies by Brohi et al.[3] and MacLeod et al.[4] identified the presence of coagulopathy early after trauma, as well as its association with increasing injury severity[3] and that it carries an associated increased risk of death.[4] Research in this area has exploded, with many research groups seeking to better elucidate the mechanisms behind this coagulopathy as well as decipher how best to treat it. The publication, in 2007, of Borgman's retrospective study demonstrating the reduction in mortality of severely injured combat soliders by transfusing large volumes of plasma[5] incited a pursuit to validate this treatment strategy for traumatic coagulopathy.

In this article, we will seek to describe the current understanding of coagulopathy in the setting of trauma including its mechanisms, diagnosis, consequences, and treatment strategies.

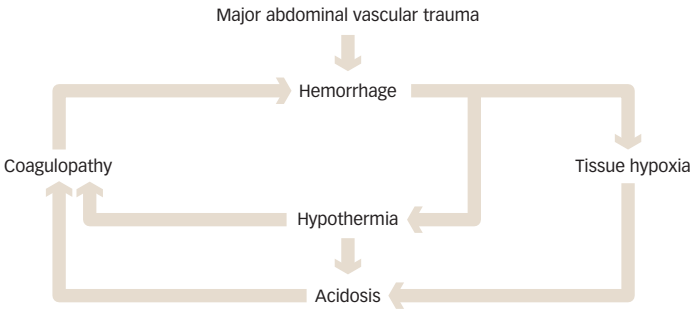
Nomenclature

The coagulopathy seen in trauma patients is currently referred to in the literature by many names. The terms trauma-induced coagulopathy (TIC),[6] early trauma-induced coagulopathy (ETIC),[7] acute traumatic coagulopathy (ATC),[3] endogenous acute coagulopathy (EAC),[8] systemic acquired coagulopathy (SAC),[8] acute coagulopathy of trauma shock (ACoTS),[9] and disseminated intravascular coagulation (DIC) with fibrinolytic or thrombotic phenotypes[10] have all been used to describe the coagulopathy seen in trauma. Indeed, this variability in its definitions reflects the current uncertainty and debate over the key mechanisms responsible for it.

TIC is an overarching term used to describe the coagulopathy that is related to and occurs after traumatic injury. It is multifactorial in etiology and includes the potential contributions from medical interventions, such as hypothermia, acidosis, and hemodilution.[6]

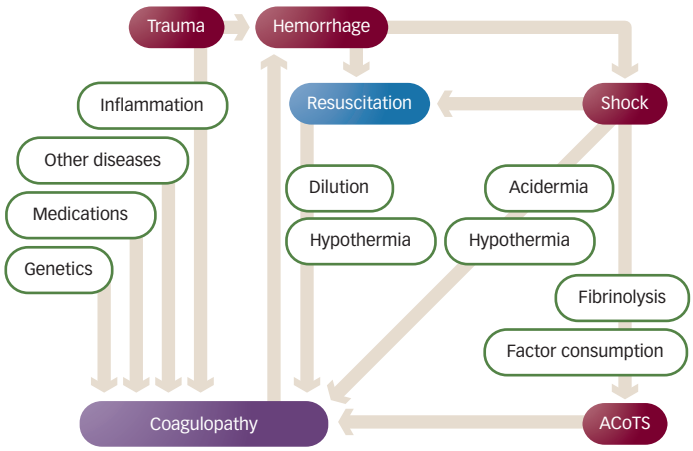
ATC was described by Brohi et al.[3] in 2003. It has most recently been characterized by a reduction in clot strength with a specific thromboelastometry signature that can be diagnosed by the CA5 (clot amplitude) parameter on ROTEM® (rotational thromboelastometry, TEM International, Munich, Germany). It can rapidly identify patients who are likely to require a massive transfusion.[11] The use of a PTr (prothrombin time ratio) >1.2 has been recommended as a clinically relevant definition of ATC.[12] EAC and ETIC are largely synonymous with ATC, as they represent changes in the coagulation system, induced by

Figure 1: Diagram of the 'Vicious Cycle' Concept



Source: Adapted from Kashuk et al., 1982.[2]

Figure 2: Diagram of Mechanisms Leading to Coagulopathy in the Injured



ACoTS = acute coagulopathy of trauma shock. Source: Adapted from Hess et al., 2008.[9]

traumatic injury, that are created independently of iatrogenic hemodilution and hypothermia.[8]

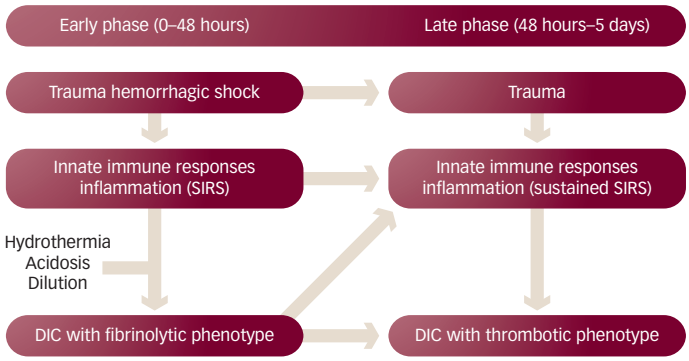
The modification of the term ATC to ACoTS represents the incorporation of the important role of tissue hypoperfusion, or shock, into the model[9] (see *Figure 2*).

DIC, although described as early as the 19th century, was only given an international working definition and scoring system in 2001.[13] Trauma has long been acknowledged as a cause of DIC,[13,14] but only recently has the early coagulopathy found in trauma been characterized as a fibrinolytic phenotype of DIC[10] (see *Figure 3*).

SAC is described as the coagulopathy associated with acidosis, hemodilution, and hypothermia,[8,15] but is mechanistically distinct from EAC.[8] EAC can lead to SAC (see *Figure 4*).

The definition of these coagulopathies has so far been largely based on international normalized ratio (INR) and partial thromboplastin time (PTT). It should be noted that these traditional tests used worldwide are coarse screening tests for coagulopathy in trauma. Studies examining clotting factor levels[7,16] and viscoelastic tests such as thromboelastometry[11] have demonstrated significant coagulopathy that is not revealed with traditional

Figure 3: Diagram of Mechanisms of Disseminated Intravascular Coagulation Leading to the Fibrinolytic Phenotype



DIC = disseminated intravascular coagulation; SIRS = systemic inflammatory response syndrome. Source: Adapted from Gando et al., 2011.[10]

INR and PTT. Indeed, a recent consensus conference acknowledged the important unique information that these tests provide in assessing coagulation.[17] The assessment and description of these coagulopathies is increasingly turning to thrombelastometry[11,18] and serum protein levels,[7,10,16] for investigation, characterization, and even clinical diagnosis.

Mechanism of Trauma-related Coagulopathy

Mechanistically, it is useful to understand that trauma itself induces changes in the coagulation and inflammatory systems.[19] Similarly, the treatment of the trauma patient can induce changes specifically related to the treatments used—i.e., large volumes of room temperature, low pH (5.5), 0.9 % saline contribute to dilution, hypothermia, and acidosis (see *Figure 1*). In addition, anaerobic cellular metabolism induced by tissue hypoperfusion (largely as a result of hypotension and hypovolemia) produces its own deleterious effects on the inflammatory and coagulation cascades (see *Figure 2*).

Complete details of the many proposed mechanisms are beyond the scope of this article, but can be found in the papers by Frith et al.,[6] Hess et al.,[9] and Gando et al.[10] However, we will discuss the pertinent components of these mechanisms. It should be noted that all research groups do agree that the hemostatic process is dynamic and in constant flux.[6,8,10]

Investigation of the coagulation system has been marked by the assessment of many serum biomarkers and protein activities. Thus far, important findings in the setting of early coagulopathy include decreased clotting factor activities,[7,16] decreased protein C activity,[20,21] antithrombin deficiency,[22] elevated cytokine levels,[22] a catalytic role of hypoperfusion,[21,23] presence of increased fibrin degradation products,[16,20] hyperfibrinolysis,[24,25] and changes in the endothelial surface layer.[6,26] Which of these findings are sentinel for the progression to lethal coagulopathy is as yet unknown.

The description of ATC as separate from DIC is controversial.[27] The research group led by Gando proposes that the coagulopathy seen in trauma is actually different phenotypes of DIC (see *Figure 3*). However, two recent studies—one clinical[22] and one anatomopathologic[28]—failed to find convincing evidence of DIC. The International Society on Thrombosis

and Haemostasis developed a working definition and scoring system[13] in 2001 to evaluate for the presence of DIC, and additional criteria have been developed by the Japanese.[29] However, none of these three systems were developed specifically for traumatic coagulopathy. Ongoing research is needed to clarify, and hopefully one day unify, the various proposed models of coagulopathy in trauma.

Who Develops Trauma-related Acute Coagulopathy?

Retrospective analyses of trauma registries in the UK,[3] US,[4,30] Germany,[31] and Canada[32] have identified the presence of acute coagulopathy upon arrival to hospital in a significant proportion of trauma patients as well as a number of predictors for its presence. The incidence of an INR or PTT result above the normal range in trauma patients is between 12–36 %, depending on the severity of injury. The study by Hess et al elegantly depicts the relationship between increasing injury severity score (ISS) and incidence of acute coagulopathy.[30] The predictors for the presence of acute coagulopathy include increased ISS,[3,30,31] hypotension,[31] acidosis,[31,32] hypothermia,[31,32] and penetrating mechanism.[32] Importantly, the presence of acute coagulopathy, even in the presence of other risk factors, has been demonstrated to be an independent predictor of death.[4]

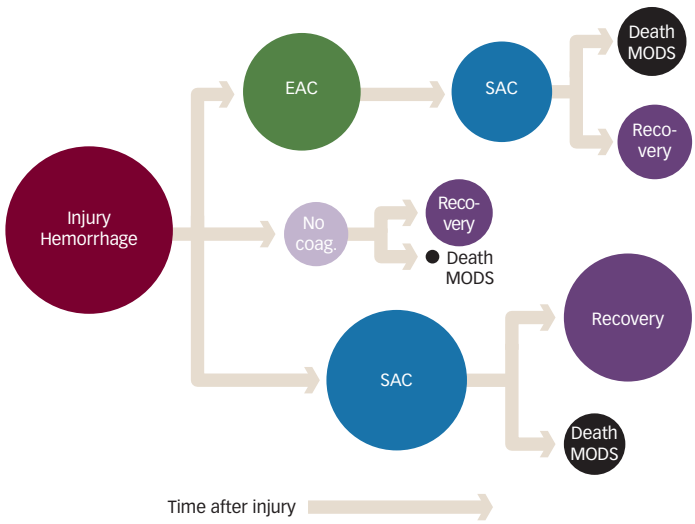
The diagnosis of acute coagulopathy can be seen in traditional tests such as INR and PTT, but their sensitivity is often low[16] and the results often take >30 minutes.[11] Viscoelastic tests such as TEG® (thromboelastrograph, Haemoscope, Niles, Ilinois, US) and ROTEM are increasingly being used to characterize and define these coagulopathies[11] as well as predict those likely to require massive transfusion.[11] TEG and ROTEM are emerging as the only truly viable modality to provide timely meaningful information to the bedside treating clinician.[6]

Natural History of Trauma-related Acute Coagulopathy

The natural history of trauma-related coagulopathy is not entirely defined. While the development of the bloody vicious cycle is well documented, exactly which patient will proceed down this path is unclear. Although the mortality rate is increased for patients in the presence of an acute coagulopathy after trauma, the rate is certainly not 100 %. Nevertheless, the presence of ATC is a severe physiologic burden on the body, with higher rates of multi-organ failure and consequently mortality, as demonstrated in a study of 8,724 patients from the German Trauma Registry.[33]

Engels et al. described 287 patients with early coagulopathy and followed their clotting parameters for the first 24 hours of admission.[32] Of these, 64 % developed worsening coagulopathy despite a mean transfusion of five units of fresh frozen plasma (FFP) during this period. However, 36 % improved with a mean transfusion of 1.8 units of FFP. A multivariate analysis demonstrated increased volume of crystalloid given in the emergency department and increased AIS (abbreviated injury scale) abdomen score to be associated with the progression of coagulopathy. Of the 287 patients, 146 (51 %) did not receive any FFP during their first 24 hours of admission and 76 (52 %) had their coagulopathy self-correct (n=67) or stabilize (n=8). In addition, the authors identified a cohort of 271 patients who had a normal INR in the trauma room but developed a coagulopathy within the first 24 hours of hospitalization. Floccard et al. studied the presence of on-scene and emergency department coagulation abnormalities.[20] Of 45 patients with on-scene coagulopathy, the coagulopathy had resolved in two patients by the time they arrived in the emergency department. While longer follow-up data were not presented, this confirmation of the ability of certain patients to self-rectify their coagulopathy is important.

Figure 4: Diagram of Development and Detection of Coagulation Abnormalities After Severe Trauma



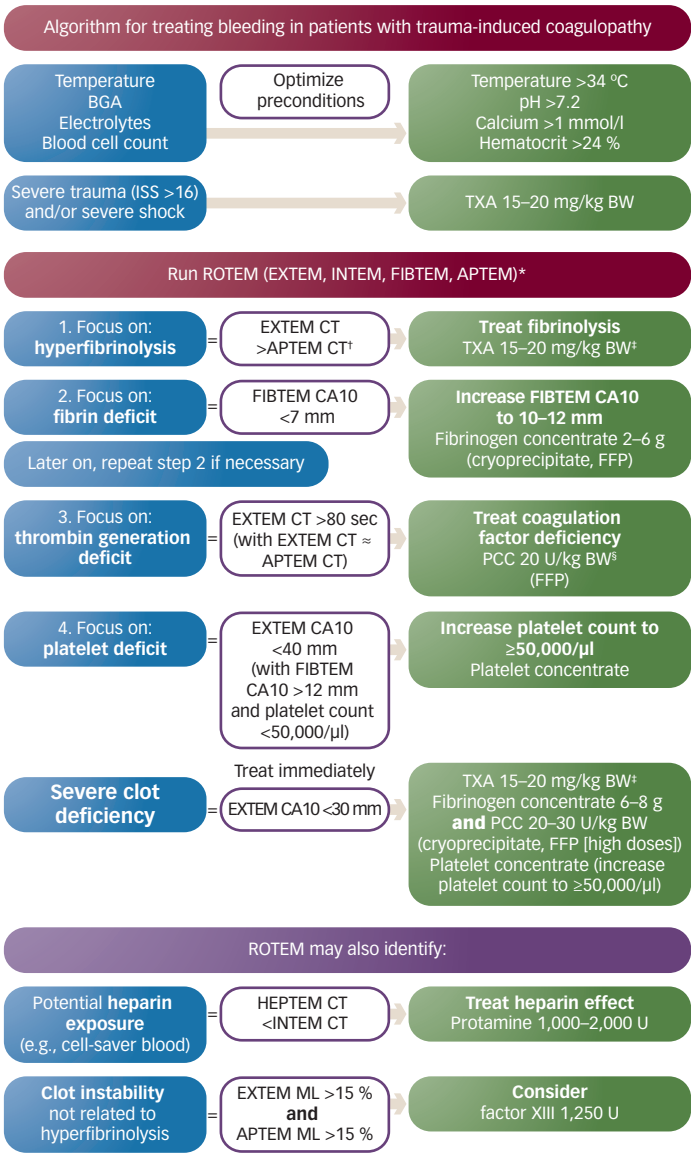
EAC = endogenous acute coagulopathy; MODS = multiple organ dysfunction system; SAC = systemic acquired coagulopathy. Source: Adapted from Cohen and West, 2011.[8]

There is no doubt that the development of an acute coagulopathy after traumatic injury portends a negative prognosis, and although the majority of patients will see their coagulopathy worsen over the next 24 hours, a significant proportion will resolve this coagulopathy independently of blood product transfusion. Clarifying which of these patients require treatment of their early coagulopathy is an important first step. The decision to initiate high-volume transfusion of blood and blood products for an isolated initial INR>1.2 is too simplistic an approach with the possibility of incurring additional complications, and would be of dubious validity in many circumstances.

Fibrinolysis can be detected by both TEG and ROTEM, and has been demonstrated to occur early in a proportion of severely injured trauma patients. Its occurrence is associated with massive transfusion requirements, coagulopathy, and hemorrhage-related death.[25,34] Whether this finding is a novel component of ATC or the phenotype of 'fibrinolytic DIC' is currently debated.[10,35] Nevertheless, the finding of mortality rates >70 % in those who develop hyperfibrinolysis[25] is important in the identification and potential treatment of these patients. The results of the CRASH-2 trial corroborate the potential important role of hyperfibrinolysis in ATC.[36]

The role of the endothelium in the setting of traumatic coagulopathy is under active investigation, with research thus far demonstrating important alterations in this heretofore neglected component.[22] Studies demonstrating association between sympathoadrenal activation and biomarkers of tissue damage[37] further support the link

Figure 5: A ROTEM®-guided Treatment Algorithm in Use at the AUVA Trauma Hospital in Salzburg, Austria



*The algorithm represents standard operating procedure for ROTEM-guided haemostatic therapy upon admission of trauma patients to the emergency room. In parentheses: haemostatic agents suggested for use in clinics where coagulation factor concentrates are not available. *For patients who are unconscious or known to be taking platelet inhibitor medication, multiplate tests (adenosine diphosphate test, arachidonic acid test and thrombin receptor activating peptide-6 test) are also performed. §If decreased ATIII is suspected or known, consider co-administration of ATIII. †Any major improvement in APTEM parameters compared with corresponding EXTEM parameters may be interpreted as a sign of hyperfibrinolysis. ‡Only for patients not receiving TXA at an earlier stage of the algorithm. Traumatic brain injury: platelet count 80,000–100,000/µl. Normal values: EXTEM/APTEM CT: 38–79 seconds; EXTEM/APTEM CA10: 43–65 mm; EXTEM/APTEM ML <15 %; FIBTEM CA10: 7–23 mm; INTEM CT: 100–240 seconds. BGA = blood gas analysis; BW = body weight; CA10 = clot amplitude at 10 minutes; CT = clotting time; FFP = fresh frozen plasma; ISS = injury severity score; ML = maximum lysis; PCC = prothrombin complex concentrate; TXA = tranexamic acid; U = unit. Source: Adapted from Schöchl et al., 2012.[18]*

of coagulopathy with inflammation.[10,19] The infusion of albumin can maintain mechanical and chemical stability of the endothelial surface layer and may be the simplest initial treatment.[26] Interestingly, albumin is found in small quantities of blood products such as plasma and packed red blood cells, which are both used liberally in damage control resuscitation.[38]

Treatment

When treating a coagulopathy related to trauma, it is important to be cognizant of the many contributing factors in its development. It is also useful to distinguish 'blind' versus 'targeted' strategies.

All patients with ATC do not require massive transfusion; indeed, the incidence of ATC is approximately one quarter of trauma patients[3,4,32,33] and the civilian incidence of massive transfusion is 2–3 %.[17] In addition, the term 'massive transfusion' needs to be rapidly discarded, as it inaccurately represents the clinical problem of massive bleeding.[17,39] Our clinical assessment tells us if a patient is massively bleeding, not if they are going to require a massive transfusion. However, massive bleeding is almost certainly going to require treatment with blood and blood products, and potentially qualify as a 'massive transfusion'. As a matter of fact, even the definition of massive transfusion across studies is inconsistent.[40,41,42] When we search for accurate ways to predict ATC, we must acknowledge that we are in fact looking for markers of clinical shock or high-risk mechanisms and injury patterns that are associated with massive/significant bleeding. The diagnosis of ATC is based on a laboratory assessment of the blood; everything else is a surrogate.[43]

The treatment of massive bleeding—or the use of massive transfusion—is intertwined with the concept of trauma-related coagulopathy. The acute coagulopathy of trauma is a discrete disease that has a decisive influence on survival, and thus the diagnosis and therapy of deranged coagulation should start as soon as possible.[44] The creation of massive transfusion (or hemorrhage) protocols (MTPs) was in response to the logistical challenges of providing adequate coagulation therapy to patients who are exsanguinating. It takes time to mobilize and make blood products available for quick administration, and therein lies the value in minimizing treatment delays that could increase patient mortality. In the classic advanced trauma life support model of resuscitation,[45] the administration of plasma would occur only after the receipt by the clinician of an abnormal coagulation parameter, which occurs at best 30–45 minutes after being drawn.[11,41] The clinician would then request plasma, and this would typically take an additional 30–45 minutes to arrive.[46] By this time, the patient has likely received multiple litres of crystalloid fluid and sustained another period of 60–90 minutes of coagulopathic bleeding. When patients are finally administered plasma, the state of their coagulation milieu is completely different than the coagulation parameter indicated when it was drawn over one hour earlier, leading to an ongoing lag in appropriate treatment.

In response to this challenge, many researchers have sought to develop prediction models so that patients can be identified early and thus an MTP can be triggered.[39,47–53] Two additional studies have developed scores to predict coagulopathy.[54,55] However, none of these scores has been demonstrated to predict, with acceptable accuracy, the need for massive transfusion or the presence of coagulopathy.[43]

Damage control resuscitation, a recently development treatment paradigm,[56–58] includes the central tenants of permissive hypotension, minimization of crystalloid use, hemostatic resuscitation, and the use of damage control surgery.[38] In this manner, resuscitation is targeted to provide adequate organ perfusion (not a 'normal' blood pressure) in order to decrease fluid requirements, prevent possible clot dislodgement

prior to definitive surgical/angiographic control of bleeding, avoid iatrogenic hemodilution and acidosis, and provide early correction of ATC. This treatment modality is independent of patient location and begins at the scene with pre-hospital providers, and continues with the patient on their journey through the emergency department, operating/angiography room and intensive care unit. Nevertheless, there is a limit to permissive hypotension.[59,60] Failure to restore normal perfusion by a certain threshold, perhaps 60–90 minutes, will likely create significant tissue damage of its own accord and only exacerbate the process that the permissive hypotension was attempting to abate. The evidence supporting this approach is growing with a demonstrated survival benefit recently reported[61,62] and further studies are ongoing.[62]

Although there has been much fascination in the literature with the optimal ratio of blood product transfusion strategies (i.e., 1:1:1 versus 1:2-3), it is important to note that all of these strategies are 'blind'. The efficacy of high-volume plasma transfusion treatment is predicated on their early use in the setting of massive bleeding and ATC to reverse or abate this process. Once a patient is identified as being at high risk of requiring a massive transfusion, the trigger is pulled, the boxes of blood products start arriving, and the treatment continues until a clinical decision is made that the patient's bleeding has been controlled and their coagulopathy has been corrected. The ability of conventional coagulation tests (INR, PTT) to provide meaningful realtime guidance in the treatment of a massively bleeding patient is being increasingly refuted.[18,34,41]

The use of 'targeted' treatment strategies refers to making the decision and selection of the hemostatic intervention based on realtime whole blood clotting information as currently provided by viscoelastic tests such as TEG or ROTEM. In North America, this typically means deciding on when to administer plasma, platelets, cryoprecipitate, and tranexamic acid; in Europe, the use of factor concentrates—including fibrinogen, factor XIII, and prothrombin complex—are also options.[18] In the setting of difficulty in predicting the presence of coagulopathy and the need for massive transfusion, with the known adverse affects of unnecessary blood product transfusion, the value of a point-of-care coagulation assessment such as TEG or ROTEM that is able to discriminate the need for massive transfusion within five minutes is self-evident, especially when this information allows the specific targeting of the abnormal aspects of the coagulation milieu and the tailoring of blood product administration (see *Figure 5*).

The side effects of blood product transfusion, which include systemic inflammatory response syndrome, acute respiratory distress syndrome, multi-organ failure, sepsis, and circulatory overload,[63–65] have been well documented. Furthermore, blood is also a precious resource, and its wastage, whether by discarding units prior to transfusion or needlessly transfusing a product to a patient, represents not only a risk to the patient but an opportunity cost to society.[66]

Further research is certainly required. Current studies are investigating the effect of blood product transfusion ratios,[67–69] the utility of TEG compared with conventional coagulation tests,[70] and the use of plasma versus factor concentrates[71]—to list a few.

Summary

The optimal treatment of trauma-related coagulopathy is early identification, avoidance of intragenic exacerbation, and early targeted treatment. Currently, viscoelastic tests possess a superior ability to identify ATC; implementing the damage control concepts of crystalloid limitation and permissive hypotension can avoid exacerbating surgical bleeding and hemodilution. Early provision of hemostatic treatments such as plasma, fibrinogen, and antifibrinolytics as directed by realtime viscoelastic tests allow individual targeted therapy and the minimization of deleterious consequences created by the indiscriminate use of blood products. This paradigm represents the state of the art in the management of trauma-related coagulopathy. ■

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