The Acute Coagulopathy of Trauma:
Mechanisms and Tools for Risk Stratification

Marc Maegele[1,2], Philip C. Spinella[3,4], Herbert Schoechl[5,6]

[1]Department of Traumatology and Orthopedic Surgery, Cologne-Merheim Medical Center (CMMC), University of Witten/Herdecke, Ostmerheimerstr. 200, D-51109 Cologne, Germany

[2]Institute for Research in Operative Medicine (IFOM), University of Witten/Herdecke, Cologne-Merheim Medical Center (CMMC), Ostmerheimerstr. 200, D-51109 Cologne, Germany

[3]St. Louis Children´s Hospital, Director Critical Care Translational Research Program, Washington University School of Medicine, Campus Box 8116, One Children´s Place, NWT 10th Floor, St. Louis, MO 63110, USA

[4]United States Army Institute of Surgical Research, Fort Sam Houston, TX 78234-6315, USA

[5]Department of Anaesthesiology and Intensive Care, AUVA Trauma Hospital, Dr. Franz-Rehrl-Platz 5, A-5010 Salzburg, Austria

[6]Ludwig Boltzmann Institute for Experimental and Clinical Traumatology, Donaueschingenstr. 13, A-1200 Vienna, Austria

Correspondence to:

Prof. Dr. med. Marc Maegele (M.D., Ph.D.)

Department of Traumatology and Orthopedic Surgery

Cologne-Merheim Medical Center (CMMC)

University of Witten/Herdecke

Ostmerheimerstr. 200, D-51109 Cologne, Germany

Telephone: +49-221-8907-13614; FAX: +49-221-989-5721

E-Mail: Marc.Maegele@t-online.de

Abstract

Trauma remains the leading cause of death with bleeding as the primary cause of preventable mortality. When death occurs it happens quickly, typically within the first 6 hours after injury. The principle drivers of the acute coagulopathy of trauma have been characterized but another group of patients with early evidence of coagulupathy both physiologically and mechanistically distinct from this systemic aquired coagulopathy has been identified. This distinct phenotype is present in 25-30% of patients with major trauma without being exposed to the traditional triggers and is associated with higher morbidity and a fourfold increase in mortality. Despite improvements in the resuscitation of exsanguinating patients, one of the remaining keys is to expeditiously and reproducibly identify the patients most likely to require transfusion including massive transfusion (MT) with damage control resuscitation principles. Several predictive scoring systems/algorithms for transfusion including MT in both civilian and military trauma populations have been introduced. The models developed usually suggest combinations of physiologic, haemodynamic, laboratory, injury severity and demographic triggers identified on the initial evaluation. Many use a combination of dichotomous variables that are readily accessible after the patients´s arrival to the trauma bay but others rely on time-consuming mathematical calculations and may thus have limited real-time application. Weighted and more sophisticated systems including higher numbers of variables perform superior. A common limitation to all models is their retrospective nature and prospective validations are needed. Point-of-care viscoelasatic testing may be an alternative to early recognize trauma-induced coagulopathy with the risk of on-going haemorrhage and transfusion.

Introduction

Trauma is the leading cause of death world-wide in persons under the age of 40 years (1) and accounts for approximately 10% of all deaths in general (2). Despite substantial improvements in acute trauma care, uncontrolled haemorrhage is still responsible for more than 50% of all trauma-related deaths in both civilian and military settings within the first 48 hours after hospital admission (3). Haemorrhage has also been determined to be the most common cause of preventable deaths (4-6). Clinical observations together with recent research emphasize the central role of coagulopathy in acute civilian and military trauma care (7-15) but rapid identification of patients with active ongoing bleeding requiring transfusion or even massive transfusion (MT) remains unsatisfactory. Vice-versa, the early identification of trauma patients at risk for ongoing bleeding and transfusion is of fundamental clinical importance in order to rapidly address and correct the acute coagulopathy of trauma including potential triggers via early activation of damage control resuscitation (DCR) strategies, MT protocols and timely adequate mobilization of resources, for example blood bank resources in the civilian setting as well as activation of whole blood donation in the military setting (16-19).

To date, several authors have shown that early recognition of the acute coagulopathy of trauma accompanied by adequate and aggressive management including the balanced use of blood components can correct coagulopathy, control bleeding, reduce blood product use and improve outcome in severely injured patients (20-22). However, the optimum ratio of packed red blood cell concentrates (pRBCs), fresh frozen plasma concentrates (FFPs), and platelet concentrates (PCs) is still under investigation (PROPPR: Prospective Randomized Optimum Platelet and Plasma Ratios Study). As an alternative approach, other groups have reported improved survival rates by using thromelastometry guided individualized coagulation therapy based on the administration of coagulation factor concentrates (23). But also here, no

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randomized controlled study has been performed to date assessing this concept and safety data are still lacking. In this review we present the current understanding and concepts of the acute coagulopathy of trauma as well as clinically relevant strategies for its early detection. These concepts, in principle, are based upon the constructive discussions among key opinion leaders in the field during the 8th Wiggers-Bernard-Conference on „Trauma-induced Coagulopathy" held in Salzburg (Austria), February 16-18, 2011 (see also Supplement to Shock xx).

The Acute Coagulopathy of Trauma

The priniciple triggers to drive the acute coagulopathy of trauma are summarized in **Figure 1** (7,24,25). Direct loss and the consumption of coagulation factors, dilution, hypothermia, acidosis and fibrinolysis and the release of anticoagulation factors, e.g. activated protein C, all interfere with coagulation and diminish haemostasis. There seems to be an additive effect among the clinical drivers of the process as the probability of life-threatening coagulopahy increases with the number of triggers present. Cosgriff and co-workers (26), for example, have shown that the conditional probability of developing coagulopathy after trauma was 1% in moderate injury without the presence of additional triggers but increased to 39% in severe injury (ISS > 25) combined with hypotension, to 58% when injury occurred with acidosis (pH < 7.1), and to 98% in cases of ISS > 25 together with hypotension (systolic blood pressure < 70mmHg), hypothermia (<34°C), and acidosis (pH < 7.1).

Dilution may occur both physiologically and iatrogenically. In trauma-associated physiologic haemodilution, the unopposed osmotic activity of plasma in states of hypotension is prompted by a water shift into the intravascular space thus diluting plasma proteins until equilibrium is re-established. In this scenario each protein is diluted to the same amount and their interactions, for example the intrinsic „tenase complex" comprising combined factors IXa, VIIIa and X, are reduced proportionally to their individual factor concentrate changes. In this

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model, Monroe calculated a 37% reduction in single factor concentration to result in a 75% reduction in overall complex activity (27).

Iatrogenic dilution is caused by unguided and often over administration of fluids in the acute phase of trauma care. In patients from the TR-DGU database (TraumaRegistry of the Deutsche Gesellschaft für Unfallchirurgie/German Trauma Society) coagulopathy upon Emergency Room (ER) admission was observed in > 40% of patients with > 2000mls, in > 50% with > 3000 mls, and in > 70% with > 4000 mls of fluids administered during the pre-hospital phase of care (13). More recently, a pre-hospital intravenous colloid:crystalloid ratio $\geq$ 1:2 and the amount of pre-hospital intravenous fluids $\geq$ 3000 ml have been identified as independent contributors to the acute coagulopathy of trauma (25). This dilution is accompanied by consumption and inactivation not only of cogulation factor substrates but also coagulation enzymes with magnitudes matching the degree of individual injury (28).

Meng and co-workers have frequently demonstrated the effects of temperature and pH on coagulation factor and complex activity (29,30). Both, temperature and acidosis, contribute to coagulopathy by reducing the pace of plasma coagulation factor biochemical reactions. This activity is slowed down by approximately 5% with each 1°C drop in temperature. The von Willebrand-Factor (vWF)-glycoprotein Ib interaction which activates platelets is absent in 75% of individuals at 30°C (31,32). Similarly, drops in pH to values of 7.2 have been shown to reduce coagulation factor complex activities by half and down to 20% of normal activity at pH 6.8 (30). **Figure 2** shows an example for reduced plasma coagulation factor and complex activity if pH drops to values of 7.0. The correlation between the activity or activation of different coagulation factors and negative base excess (BE) assuming non-respiratory acidosis is demonstrated in **Figure 3**.

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Under physiological conditions the coagulation system modulates fibrinolysis in that blood clots are maintained stable for a given time to control bleeding and to promote adequate wound healing. High concentrations of thrombin inhibit plasmin activation via the activation of TAFI (thrombin-activated fibrinolysis inhibitor) and PAI-1 (plasminogen activator inhibitor-1). Vice-versa, if the thrombin burst is weak, TAFI remains unactivated. Furthermore, if thrombin encounters thrombomodulin on endothelial cells, protein C may be activated which then inactivates PAI-1.

Hyperfibrinolysis (HF) has been identified as a major contributor of mortality in bleeding trauma patients (33,34). For example, Schöchl and co-workers have reported a mortality rate of approximately 88% in trauma patients with hyperfibrinolysis present upon Emergency Room (ER) admission as detected by viscoelastic testing (33). Even a small reduction of the maximum amplitude in thromelastography (TEG > 15%) is likely to be associated with higher transfusion requirements including MT, coagulopathy and haemorrhage-related death (34).

Acute Coagulopathy in Trauma and Shock

More recently, it has been recognized that another group of trauma patients presents to the ER with early evidence of coagulopathy both physiologically and mechanistically distinct from this above referrenced traditional sytemic aquired coagulopathy. Several studies have identified an acute traumatic coagulopathy, according to standard coagulation tests, present in 25-30% of patients with major trauma without being exposed to the traditional triggers of coagulopathy. For example, Brohi and colleagues have reported a series of patients who had received < 500 mls of fluids during pre-hospital care of whom one out of four presented coagulopathic upon arrival to the trauma bay as indicated by a prothrombin time (PT) $\geq$ 1.5 (12). This finding was confirmed by other investigators reporting even larger patient series (13,14) and also in children (35). Our own group has reported the presence of coagulopathy

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upon admission even in trauma patients who had received no fluid resuscitation at all during their pre-hospital phase of care (13). In all studies, the presence of coaguloathy was associated with a higher magnitude of injury sustained as reflecced by higher Injury Severity Scores (ISS) as well as a dramatic increase in mortality up to two- to four-fold (12-14,35,36) (**Figure 4**). In Brohi´s study, increasing injury severity predicted a stepwise increasing fraction of patients with increased PT upon admission with presence in 45% of all patients with an ISS > 45 (12). Abnormalities in other conventional tests such as fibrinogen levels and platelet counts showed a similar stepwise increase together with increased injury severity (36). Among the 28% of the 20,000 trauma center admissions with any initial PT prologantion reported by MacLeod and colleagues, there was a 35% increase in the risk of in-hospital death; among the 8% of patients with prolonged partial thromboplastin time (PTT), the increase in risk of dying was 42% (14). Noteworthy, all of these deaths occurred within the first five hours after admission and were due to uncontrolled primary haemorrhage.

In their analysis from data from the German TR-DGU database, Wafaisade and co-workers reported an ongoing state of shock after trauma (on scene and upon admission to the trauma bay) to be associated with an almost three-fold increase in risk for the development of coagulopathy (25). **Figure 5** shows an increasing frequency of coagulopathy upon ER arrival with increasing levels of shock as reflected by base excess (BE). This finding corresponds to other reports (7,15) and has also been described in children (35). Hypoperfused tissue inducing acidemia may be one potential mechnism underlying this shock/trauma-induced coagulopathy, as acidemia interferes with with the coagulation enzyme activity (see above). More recently, several authors have shown that shock may also activate anticoagulant and hyperfibrinolytic pathways. In this context, Brohi and colleagues have suggested that, in the presence of shock and hypoperfusion, the endothelium releases thrombomodulin which complexes with thrombin to divert it into an anticoagulant function. Thus, reduced amounts of

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thrombin are available to cleave fibrinogen, and thrombin complexed to thrombomodulin may also activate protein C which inhibits the extrinsic pathway and antifibrinolytic factors (8; **Figure 6**). Of course, this relatively new identified pathway still needs further and more detailed investigation.

Thus, direct tissue trauma and shock/hypoperfusion may represent the primary drivers responsible for the development of this distict form of coagulopathy apart and independent from the traditional factors. This coagulopathy is, in addition, associated with a higher transfusion requirement, a greater incidence of multi organ dysfunction syndrome, longer ICU and overall in-hospital length-of-stays (LOSs) as well as a four-fold increase in mortality compared to those patients with normal coagulation. The early undetected presence of this distinct coagulopathy almost certainly contributes to the development and aggravation of the above mentionned coagulopathy which is considered systemically aquired and frequently observed after severe injury.

Strategies and Tools for Early Detection and Stratification of Risk

Pertubations in blood coagulation are common after major trauma and are associated with poor outcomes. A substantial proportion of trauma patients is already coagulopathic upon admission (11-14) and incidence rates up to 60% have been reported according to definition (37). The human coagulation system can be rapidly overwhelmed by severe injury (38) and death from traumatic exsanguination usually occurs early, typically within the first six to 12 hours after initial impact but heavily weighted toward the first 1-2 hours (15,39-41). Approximately 10% of all trauma patients are transfused with at least one unit of blood and up to 30% of these require massive transfusion (MT) as defined by transfusion of ≥ 10 units within the first 24 hours after Emergency Room (ER) admission (42,43). Even with improved triage, evacuation, early surgical intervention (for example Damage Control Surgery (DCS)),

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problems associated with bleeding and the inability to control it remain chellenging. The classic definition of massive transfusion is being changed by some to reflect the changing practice of early blood use with damage control resuscitation (44) and some prefer to instead focus on defining massive bleeding instead of massive transfusion. Until massive bleeding can be more accurately characterized or quantified we will continue to determine the risk of haemorrhagic death by using transfusion requirement as a surrogate.

Despite substantial improvements in the knowledge on how to adequately resuscitate the exsangiunating patient, one of the fundamental issues to improve the outcome still remains the early identification of patients in the need for transfusion including those requiring MT. Although the criteria that trigger the activation of massive transfusion protocols (MTPs) remain highly center and provider dependent, the benefits of timely MTP activation have been frequently demonstrated given the identification of appropriate patients (45,46). However, not all investigators were able to show improved survival after MTP implementation or activation (47). Allogeneic blood transfusion increased significantly without being associated with mortality. A similar oberservation was made by Simmons and colleagues (48). Therefore, early and reliable prediction of the need for MT is highly demanded.

The inappropriate use of massive transfusion protocols (MTPs) in patients not in the need of MT may result in a higher incidence of side effects of FFP and PC transfusion without an improvement in survival (49-51). Although blood transfusion has the obvious benefit of volume restoration and improved oxygen carrying capacity in the injured patient, there are quite a few risks and immunosuppressive and infectious consequences associated with blood products including transfusion reaction, transmission of blood-borne pathogens, and the impact of limited supply (52-55). For these reasons, there has been a trend to restrict transfusion in non-urgent clinical settings and to limit transfusion to ongoing and imminently

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life-threatening situations. However, the hazards of transfusion may appear somewhat trivial relative to the need of care for an exsanguinating patient.

Substantial problems in the use of conventional coagulation testing for the early identification of patients in the need for transfusion including those requiring MT include delayed turn-around times, incomplete characterization, and their poor predictive nature not accurately reflecting the patient´s true coagulation status (12,56,57). Although international normalized ratio (INR) and base deficit (BD) are good predictors of mortality, by themselves, they cannot discriminate between patients to may go or not go on for MT (58). Second, surgical relevant bleeding due to thoracic and/or retro-/ intraperitoneal organ injury is difficult to detect and often requires time consuming diagnostics (59). Thus, significant haemorrhage and coagulopathy may be underestimated or even missed during early resuscitation (14,60).

Scoring Systems and Algorithms

Over the past few years, a considerable number of scoring systems has been developed and introduced for the initial evaluation of the bleeding trauma patient in both civilian (17,45,61-69) and military seetings (70-73). The authors have just recently published a comprehensive overview of the most commonly discussed scoring systems and algorithms for the need of transfusion including massive transfusion in severely injured patients (74). These systems may provide clinically useful information that potentially gives freedom to providers to deviate from established algorithms toward the more aggressive and early use of blood products with the assumption that early product use improves outcome. These scoring systems may be used to guide the activation of massive transfusion protocols and could help providers of all experience levels know when it is likely that the patient will require a massive transfusion.

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The scoring systems developed to date usually suggest combinations of physiologic, haemodynamic, laboratory, injury severity and demographic triggers identified on the initial evaluation of the bleeding trauma patient. Many of them use a combination of dichotomous variables that are obtained rapidly after the patients´s arrival to the trauma bay but others rely on time-consuming mathematical calculations or complex scoring algorithms that are required to determine the patients who will need MT and may thus have limited real-time application.

The most commonly proposed triggers that were correlated with the need for transfusion including massive transfusion in the civilian setting are shown in **Table 1** and include systolic blood pressure which is present in 9/9 scoring systems, followed by heart rate (present in 6/9 scoring systems), haemoglobin/haematocrit (present in 5/9 scoring systems), and positive focused assessment for the sonography of trauma (FAST+; present in 4/9 scoring systems). Parameters that can be quickly obtained via point-of-care (POC) ABG (arterial blood gas)-analyzers, for example base excess/deficit (BE/BD), lactate, and pH are included in 6/9 civilian scoring systems. Six out of nine systems consider anatomical injury including its magnitude or mechanism of injury as component of their assessment. However, the severity of injury as reflected by the Injury Severity Score (ISS) or the overall pattern of the anatomical injury may be difficult to calculate and to assess during initial assessment.

A major and common limitation to all scoring systems and algorithms with one exception is their retrospective nature. All systems have been developed retrospectively based upon datasets derived from single or multi center civilian or military databases. Some models have been developed using a classical datasplit approach with half of the dataset for development and the other half for internal validation. Meanwhile, some scores and algorithms have been internally re-validated on data from the same database, for example the Trauma-associated Severe Haemorrhage-Score (TASH-Score; 62). The only score that has been prospectively

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validated on data from a subset of 481 Emergency Room (ER) patients is the Emergency Transfusion Score (ETS; 69).

To date, several systems and algorithms have been applied onto other external but also retrospective datasets and have thus been externally validated. In developing their ABC-Score Nunez and co-workers, for example, have applied both the TASH- and the McLaughlin-Scores onto their local trauma center database including 596 trauma patients for score comparison (45). In result, all three scores (TASH AUROC = 0.842; McLaughlin AUROC = 0.846; ABC AUROC = 0.842) were considered as equally good predictors for MT without a statistically significant difference between the scores. In another retrospective study, Cotton and colleagues (75) have applied the ABC-Score onto adult trauma datasets from three different Level I trauma centers in the United States (n = 513 from trauma center 1; n = 373 from trauma center 2; and n = 133 from trauma center 3) and compared the predictive ability of the score at each institution. The sensitivity and specificity for the ABC score to predict massive transfusion ranged from 75% to 90% and from 67% to 88%, respectively. Correctly classified patients and AUROCs, however, were 84% to 87% and 0.83 to 0.90, respectively. Recently, Mitra and co-workers (76) compared the performance of the PWH-Score (63) to the ABC- (45) and TASH-Scores (61,62) by a retrospective review of a subgroup of major trauma patients (n = 1.234) derived from The Alfred Trauma Registry (Victoria/Australia). In this analysis, the performance of the TASH-Score was best with an AUROC of 0.8986, followed by the PWH-Score (AUROC = 0.8419) and the ABC-Score.

Our own group has recently applied a total of six scores and algorithms to predict transfusion in trauma patients, i.e. ABC, Larson, PWH, Schreiber, TASH, and Vandromme, onto a large subset of trauma patients derived from the most up-dated database of the German TR-DGU (n = 5.047/ unpublished observation; manuscript in preparation by Brockamp et al.). This extract

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included data from adult severely injured trauma patients (ISS > 16) with all variables present from each patient to calculate all six scores. Although we had initially attempted to validate all scores on our database, the remaining scores had to be excluded from this analysis due to missing or non-captured data within our registry for model calculation. For the TASH-Score, this analysis served again as an internal validation while all other scores were externally validated by being subjected onto our datasets. Not surprisingly that the TASH-Score performed best (AUROC 0.889) followed by the PWH-Score (AUROC 0.860) which is also a weighted score with structure and content variables very similar to the TASH-Score **(Figure 7)**. In this analysis, the non-weighted and more simple scores performed less accurate (AUROCs for Vandromme-Score: 0.840; Larson-Score: 0.823; Schreiber-Model: 0.800; and ABC-Score: 0.763).

Viscoelastic Testing Methods

An alternative to scoring systems and algorithms to early recognize trauma-induced coagulopathy with the risk of on-going haemorrhage and transfusion requirement is the early use of viscoelastic testing methods. To date, similar to the above referenced scoring systems and algorithms prospective data is also limited for this approach. However, low maximum clot firmness (MCF) in thrombelastometry EXTEM (activates haemostasis via the physiological activator tissue factor), INTEM (activates the contact phase of haemostasis) and FIBTEM (an EXTEM based assay for the fibrin part of the clot) or maximum amplitude (MA, the equivalent TEG parameter) have been identified as important determinants of packed red blood cell transfusion (57,58,77-79). Cotton and colleagues (77) recently presented results from a pilot study in which they had prospectively evaluated the timeliness of real-time rapid thrombelastography results (r-TEG), their correlation with conventional coagulation tests, and the ability of r-TEG to predict early blood transfusion in 272 consecutive major trauma activations over a 5-month time period. Early r-TEG values (activated clotting time [ACT], r-

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value [reaction time = time to first evidence of a clot], k-time [time from the end of r until the clot reaches 20mm > represents the speed of clot formation]) were available within 5 minutes, late r-TEG values (maximal amplitude [MA = reflects clot strength] and α-angle [tangent of the curve made as the k is reached]) were available within 15 minutes, in contrast to results from conventional coagulation testings with turn-around times of 48 minutes on average. Activated clotting time, r-value, and k-time showed strong correlations with later incoming results from conventional testings and linear regression demonstrated activated clotting time to predict the need for red blood cells, plasma, and platelet transfusions within the first 2 hours of arrival. In addition, an activated clotting time <105 seconds predicted patients who did not receive any transfusions during the first 24 hours of admission. Similar results have been reported by Davenport and colleagues (57). In their study a threshold of clot amplitude of ≤ 35 mm at 5 minutes of rotational thrombelastometry was indicative for acute traumatic coagulopathy and the need for transfusion including massive transfusion. These findings are in concert with reports by Leemann and co-workers who demonstrated low INTEM MCF along with low haemoglobin levels to be an independent risk factor for massive transfusion (78). An overview of the most relevant studies conducted to date on the use of viscoelastic testing in the context of the acute coagulopathy of trauma including main conclusions is provided in Table 2.

Point-of-care viscoelastic testing may offer the unique potential to predict transfusion even faster as compared to scoring systems involving conventional coagulation testing and to activate and guide resuscitations more objectively. A recent retrospective analysis of major trauma patients revealed low FIBTEM amplitudes (< 4mm) and/or low EXTEM amplitudes at 10 minutes (CA 10) to be highly predictive for massive transfusion (79). Independent from the viscoelastic test used, time to effective clot formation, clot strength and sustained stability of the clot appear to have the highest clinical value. The authors have recently published a

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comprehensive review on the early and individualized goal-directed therapy for the acute coagulopathy of trauma including their local hospital algorithm for managing this potentially life-threatening disorder based on the use of viscoelastic testing (80). Other algorithms have been published elsewhere (81,82).

Conclusion

Trauma remains the leading cause of death and bleeding is the primary cause for this mortality usually occurring quickly within the first 6 hours after impact. Even with improved triage, evacuation and early surgery, bleeding-associated problems and the inability to control it remain challanging. The principle drivers of the acute coagulopathy of trauma have been identified. More recently, it has been recognized that another group of trauma patients presents with early evidence of coagulupathy both physiologically and mechanistically distinct from this systemic aquired coagulopathy and with worse outcome. One of the remaining keys is to expeditiously and reproducibly identify the patients most likely to require transfusion including massive transfusion. The scoring models developed so far usually suggest combinations of physiologic, haemodynamic, laboratory, injury severity and demographic triggers identified on the initial evaluation. Weighted and more sophisticated systems including higher numbers of variables perform superior over simple non-weighted models. A major and common limitation to all models is their retrospective nature and prospective validations are urgently needed. Point-of-care viscoelasatic testing may be an alternative to these systems to early recognize trauma-induced coagulopathy with the risk of on-going haemorrhage and transfusion.

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Figure/Table legends

Figure 1: Potential mechanisms involved in the acute coagulopathy of trauma. Besides dilutional coagulopathy, haemorrhage may also induce shock which is followed by acidemia and hypothermia further triggering coagulopathy forming the so-called „lethal triad". Trauma with shock thus causing hypoperfusion and hypoxia can also cause coagulopathy associated with further consumption and hyperfibrinolysis. The clinical importance of inflammation for the development of the acute coagulopathy of trauma is not yet fully understood (adopted and modified from (7)).

Figure 2: Example for the decrease in plasma coagulation factor/complex activity if pH drops from 7.4 to 7.0 (adopted and modified from (30)).

Figure 3: Correlation between activity/activation of different plasma coagulation factors and negative base excess assuming non-respiratory acidosis (adopted and modified from (30) and (83), and Rolf Zander (Mainz/Germany)).

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Figure 4: Mortality in patients with and without coagulopathy upon ER admission with respect to the magnitude of injury sustained (adopted and modified from (13)).

Figure 5: The frequency of coagulopathy as a function of shock (reflected by base excess (BE)) present upon Emergency Room (ER) admission (adopted and modified from (11)).

Figure 6: Immediate activated protein C-mediated coagulopathy (hypocoagulability) during shock and hypoperfusion. Combined trauma and hypoperfusion may lead to a hypocoagulable state via formation of an anticoagulant complex (thrombin-thrombomodulin-complex) which activates protein C to protein C active which leads to an inactivation of the coagulation factors Va and VIIIa. Activated protein C in surplus also consumes PAI-1 (plasminogen-activator-inhibitor 1) which may lead to an increase in tissue plasmonogen activator (tPA) together with hyperfibrinolysis and an increase in d-dimer concentrations (according to (8)).

Figure 7: Performance of six scoring systems to predict on-going haemorrhage and transfusion requirement upon ER arrival when subjected to a cohort of trauma patients derived from the German TR-DGU database (n = 5.147; unpublished observations; manuscript in preparation by Brockamp et al.).

Table 1: Overview of scoring systems and algorithms for the need of transfusion including massive transfusion derived from civilian datasets.

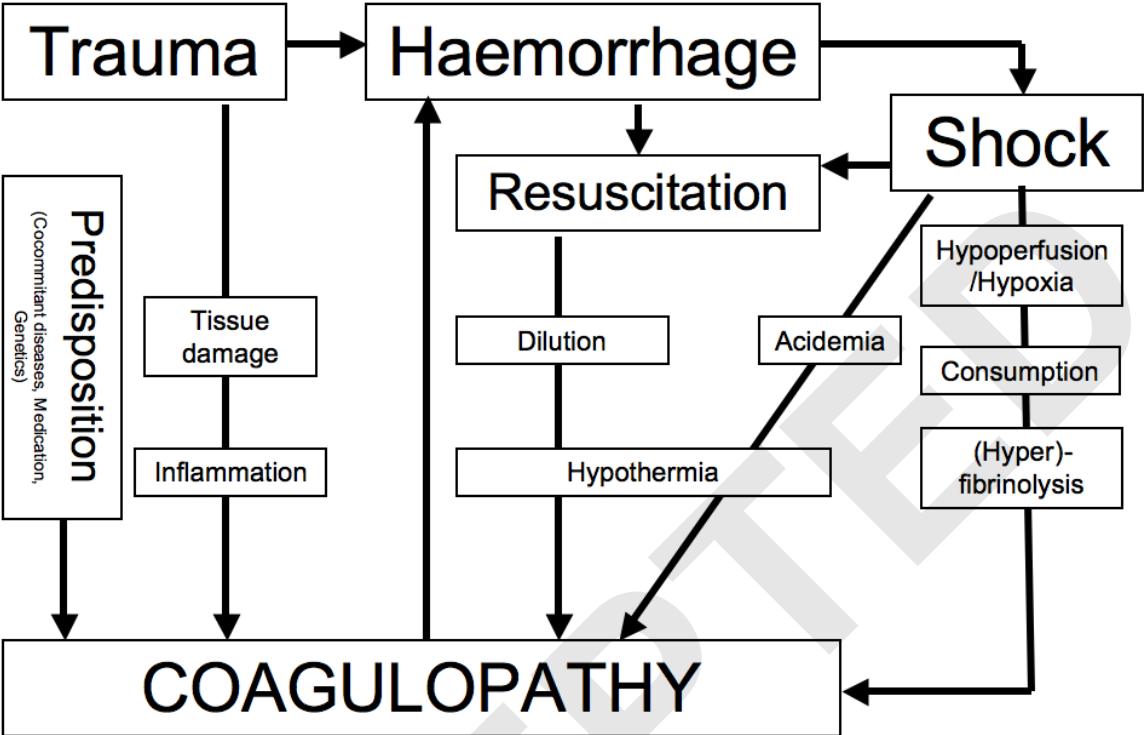**Table 2: Overview of the most relevant studies conducted on the use of viscoelastic testing in the context of the ACT.**
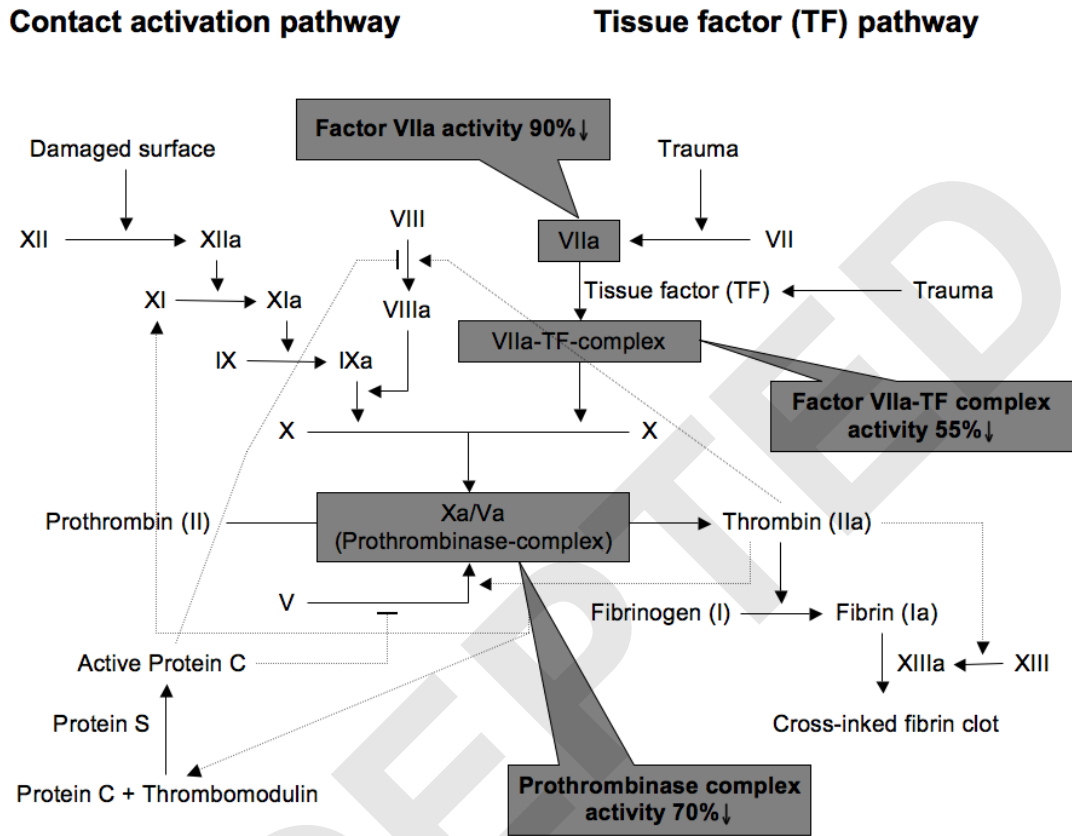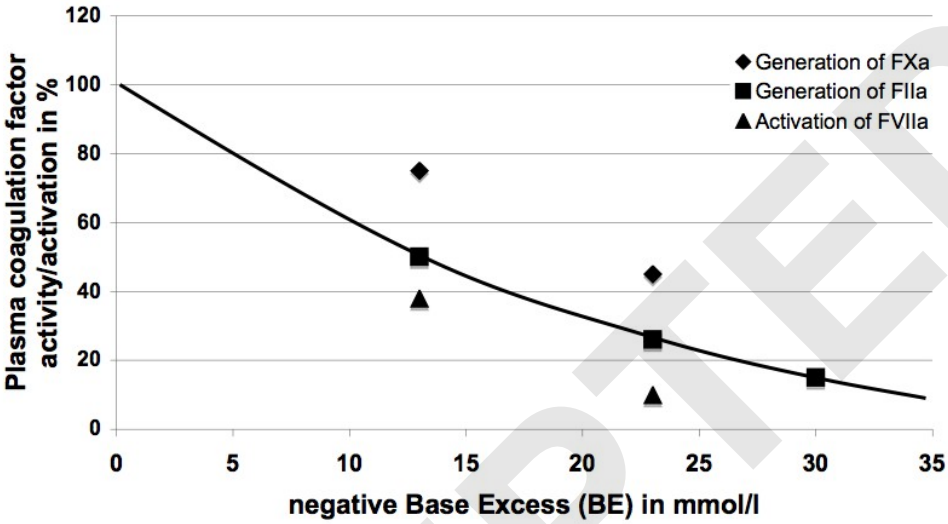
Figure 1

Figure 2

Contact activation pathway

Tissue factor (TF) pathway

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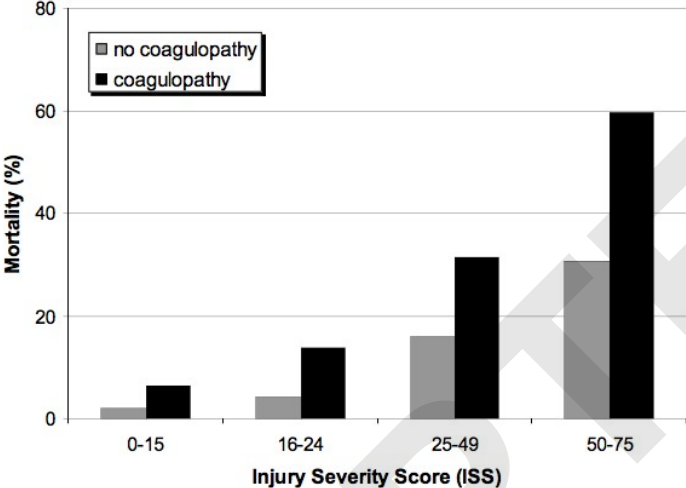
Figure 3

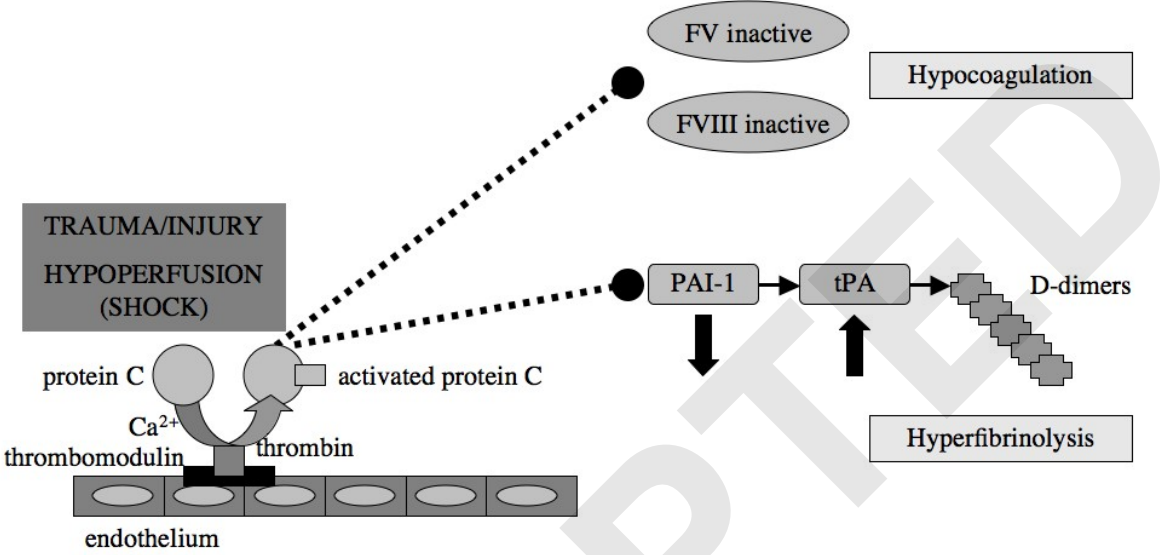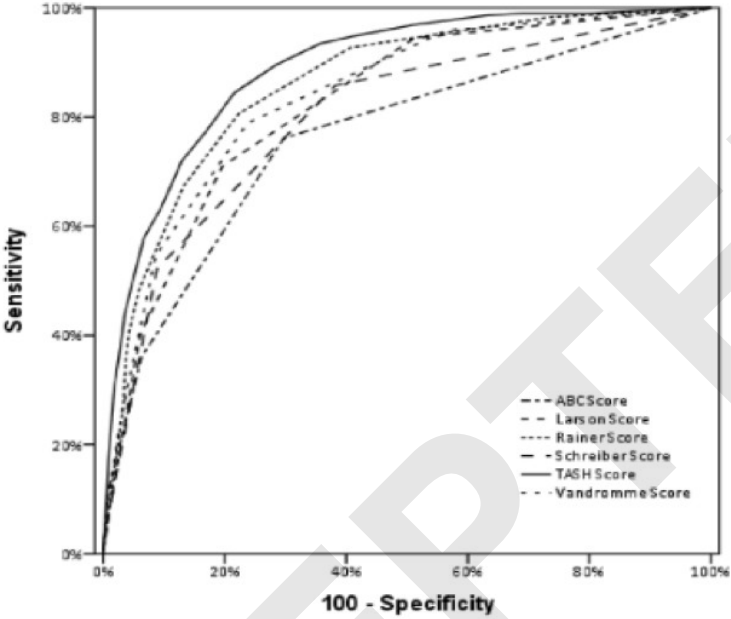**Figure 4**

Figure 5
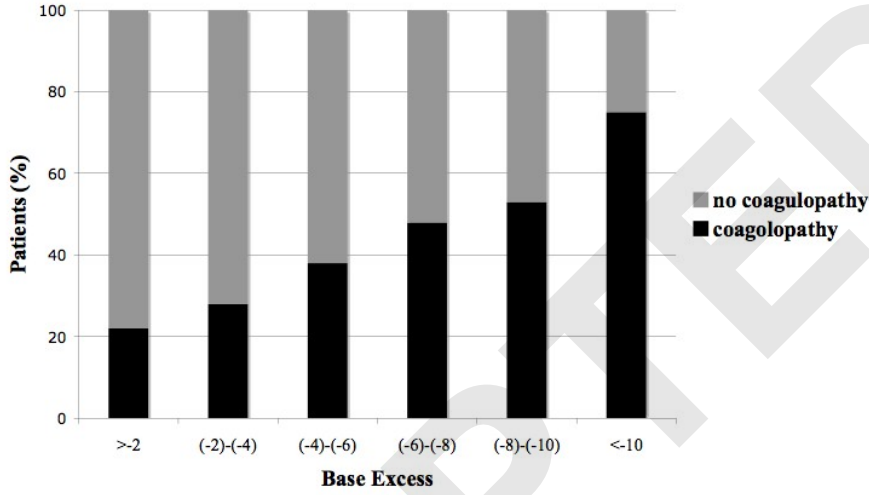
Figure 6

Figure 7

Table 1

Score	ABC (45)	TASH (61,62)	PWH (63)	Vandromme (64)	Wade (65)	Moore (66)	Baker (67)	ETS (68,69)	Individual Transfusion Triggers (17)
Design	retrospective non-weighted, dichotomous	retrospective weighted	retrospective weighted	retrospective non-weighted, sum predictors	retrospective prediction formula	retrospective prediction formula	retrospective non-weighted, sum risk factors	retrospective/ prospective weighted	retrospective individual triggers
Number of Patients	596	6.044 [61] 5.834 [62]	1.891*	514	838	383	654**	1.103 (re) [68] 481 (pro) [69]	170
Setting	civilian, single center	civilian, multi center	civilian, single center	civilian, single center	civilian, multi center	civilian, multi center	civilian, multi center	civilian, single center	civilian, single center
Parameter in Score	SBP (mmHg) HR (bpm) FAST+ Penetrating Trauma	SBP (mmHg) HR (bpm) Hb (g/dl) BE (mmol/l) FAST+ Pelvic # or/and Extremity # male	SBP (mmHg) HR (bpm) Hb (g/dl) BD (mmol/l) FAST+ GCS Pelvic #	SBP (mmHg) HR (bpm) Hb (g/dl) Lct (mmol/l) INR	SBP (mmHg) HR (bpm) Hct (%) pH	SBP (mmHg) pH ISS	SBP (mmHg) HR (bpm) High risk injury*** GCS	SBP (mmHg) FAST+ Traffic accident Fall > 3 meters Pelvic # Age Direct admission	SBP (mmHg) Hb (g/dl) BD (mmol/l) Temp (ºC) INR

* 95% of patients Chinese origin; ** large Hispanic and indigent population; ***high risk injury = trauma to the ventral chest between the midclavicular lines, abdominal injury with diffuse tenderness, survival of a vehicular crash in which another occupant died, vehicular ejection, or penetrating torso injury

BD = base deficit; BE = base excess; FAST = focused assessment for the sonography of trauma; GCS = Glasgow Coma Scale; Hct = haematocrit; Hb = haemoglobin; HR = heart rate; INR = International Normalized Ratio; ISS = Injury Severity Score; Lct = lactate; SBP = systolic blood pressure; Temp = temperature

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Table 2

Author	Year	n	Main Findings
Plotkin (58)	2008	44	TEG more accurately indicates blood product requirement than PT, PTT
Leemann (78)	2010	53	Hb ≤ 10g/dl and an abnormal MCF by ROTEM on admission reliably predicts the need for MT
Doran (84)	2010	31	ROTEM detects more abnormalities in the coagulation status than the standard laboratory tests PT and PTT
Cotton (77)	2011	583	ACT predicts red blood cell, plasma, and platelet transfusions within first 2 hours after ED arrival
Davenport (57)	2011	300	At a threshold of clot amplitude at 5 min of ≤ 35 mm, ROTEM can identify acute traumatic coagulopathy at 5 min and predicts the need for MT
Schoechl (79)	2011	323	Low FIBTEM predicts MT
Schoechl (85)	2011	88	FIBTEM MCF < 7 mm results in 9-fold increase in mortality
Petzold (86)	2012	80	TEG clot strength (G) provides consistent, independent prediction for MT and MT-death early in the resuscitation of injured patients
Nystrup (87)	2012	89	Low clot strength on admission is independently associated with increased 30-day mortality in trauma patients
Tauber (88)	2012	334	EXTEM MCF is independently associated with early mortality, MCF FIBTEM with the need for red blood cell transfusion

ACT = activated clotting time; ED = Emergency Department; Hb = haemoglobin; INR = International Normalization Ratio; MCF = maximum clot firmness; MT = massive transfusion; PT = prothrombin time; PTT = partial thromboplastin time; ROTEM = Rotational Thrombelastometry; TEG = Thrombelastography