Received: 16 April 2020 | Revised: 13 June 2020 | Accepted: 14 June 2020

DOI: 10.1111/trf.16074

REVIEW

TRANSFUSION

Viscoelastic monitoring in trauma resuscitation

Andrew C. Sayce | **Matthew D. Neal** | **Christine M. Leeper**

Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

Correspondence
Matthew D Neal, Department of Surgery, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213.
Email: nealm2@upmc.edu

Abstract

Background: Traumatic injury results in both physical and physiologic insult. Successful care of the trauma patient depends upon timely correction of both physical and biochemical injury. Trauma-induced coagulopathy is a derangement of hemostasis and thrombosis that develops rapidly and can be fatal if not corrected. Viscoelastic monitoring (VEM) assays have been developed to provide rapid, accurate, and relatively comprehensive depictions of an individual's coagulation profile. VEM are increasingly being integrated into trauma resuscitation guidelines to provide dynamic and individualized guidance to correct coagulopathy.

Study Design and Methods: We performed a narrative review of the search terms viscoelastic, thromboelastography, thromboelastometry, TEG, ROTEM, trauma, injury, resuscitation, and coagulopathy using PubMed. Particular focus was directed to articles describing algorithms for management of traumatic coagulopathy based on VEM assay parameters.

Results: Our search identified 16 papers with VEM-guided resuscitation strategies in adult patients based on TEG, 12 such protocols in adults based on ROTEM, 1 protocol for children based on TEG, and 2 protocols for children based on ROTEM.

Conclusions: This review presents evidence to support VEM use to detect traumatic coagulopathy, discusses the role of VEM in trauma resuscitation, provides a summary of proposed treatment algorithms, and discusses pending questions in the field.

1 | INTRODUCTION

1.1 | Trauma resuscitation

Trauma is a leading cause of death and disability worldwide.[1] Mortality from trauma is classically described as occurring in a trimodal distribution: immediate (minutes), early (hours), and late (weeks).[2] Although the time-to-death histogram has shifted in the last four decades, the majority of deaths still occur within 24 hours of injury.[3–5] Hemorrhage is the driving factor in approximately 50% of these early deaths, and hemorrhagic shock occurring in this window is a major contributor to delayed organ failure and late mortality.[6] Trauma-specific hemostatic dysfunction, *i.e.* trauma-induced coagulopathy (TIC), is an umbrella term that encompasses multiple mechanisms of failing hemostasis as well as later thrombotic complications.[7] TIC develops immediately after injury and is independent of other known contributors to coagulopathy including environmental exposure and crystalloid resuscitation.[7–11] Patients who develop TIC are at increased risk for death,[7] increased transfusion requirements and delayed complications including organ failure and sepsis.[10–12]

Prompt and appropriate resuscitation, in coordination with control of hemorrhage, is a key target in all injured patients. Resuscitative strategies have moved away from a

crystalloid-centric approach and toward a focus on restoration of hemostasis through damage control resuscitation (DCR). The principal tenants of DCR are (a) hemorrhage control, (b) permissive hypotension, and (c) prevention/correction of TIC.[13] Hemorrhage control is achieved in the operating room or interventional radiology suite. Permissive hypotension (systolic blood pressure <90) in both blunt and penetrating trauma is proposed to facilitate hemostasis through reduced pressure on new clot and has been shown to decrease mortality in adults compared to resuscitation to normotension.[14–18] Mitigation of TIC via appropriate blood product transfusion and optimal critical care is necessary to prevent further blood loss and curtail any hemostatic or inflammatory derangements. DCR treatments run in parallel to achieve the goal of stopping further blood loss and restoring blood volume with biologically useful substrate.

Empiric transfusion ratios of packed red blood cells (RBCs), platelets (PLT), and fresh-frozen plasma (FFP) have received considerable attention in adult[19–23] and to a lesser extent in pediatric patients.[24–28] Studies generally support increased plasma ratios with most authors favoring a "balanced" (1:1:1) strategy although superiority of a specific ratio has not obtained consensus.[29,30] As an alternative to component transfusion, early data suggest some benefit to cold-stored low titer group O whole blood transfusion in trauma patients.[31–34] The importance of timely correction of homeostasis is demonstrated through benefit of pre-hospital administration of blood products[35,36] particularly in the setting of transport times.[37,38] In supplement to empiric transfusion strategies, individualized goal-directed transfusion[39–41] has been proposed and will be discussed in this review.

1.2 | Assays for active monitoring of resuscitation

Success of a monitored resuscitation strategy is heavily dependent upon the assay(s) used to guide decision making. We will briefly discuss the rationale and interpretation of conventional coagulation tests (CCTs) and viscoelastic monitoring (VEM) assays in the context of injured patients. Further details on interpretation and science supporting these tests can be found in additional articles in this supplement.

1.2.1 | Conventional coagulation tests in trauma-induced coagulopathy

CCTs including international normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, and platelet counts are routinely used in perioperative assessment of hemostatic function and are therefore familiar to the clinician. INR $\geq$ 1.3 has been used to define TIC in adults and children,[10,11] and is associated with increased mortality and functional disability.[42–47] Prolonged aPTT, low fibrinogen, and altered platelet function have similarly been correlated with poor outcomes in pediatric[46,48,49] and adult[49–52] trauma patients. Although CCTs benefit from familiarity of interpretation, they are of limited sensitivity and specificity in predicting response to resuscitation,[53] they are not reliably associated with clinical coagulopathy, and were not developed for evaluation of TIC.[54–56] Furthermore, these plasma-based tests do not account for the contribution of the endothelium, platelets, and other critical components of hemostasis and known contributors to TIC. Of crucial importance in trauma patients, CCTs suffer from turn-around times of 30 to 60 minutes[57,58] and are therefore unable to effectively guide resuscitation in the injured/hemorrhaging patient with dynamic hemostatic dysfunction evolving over the course of minutes.

1.2.2 | Viscoelastic monitoring

In contrast to CCTs, VEM assays are whole blood tests that provide data describing the kinetics of a clot: from time to clot formation (fibrin cross-linking), to maximal clot strength (platelet function), and finally clot breakdown (fibrinolysis).[59] VEM assays can be utilized at the point of care, with results useful in guiding resuscitation available within 5 minutes.[57,60] The two primary platforms for such tests are thromboelastography (TEG, Haemonetics) and thromboelastometry (ROTEM, Tem International GmbH). The first mention of VEM evaluation of injured patients dates from 1977[61]; however, the first formal study to suggest possible use in guiding trauma resuscitation was not published until two decades later.[62] Based on the substantial body of literature that has accumulated since that time, VEM has been incorporated into the American College of Surgeons' Advanced Trauma Life Support recommendations.[63] VEM availability is suggested in all US level 1 and level 2 trauma centers; however, utilization remains low with only 9% to 18% of sites incorporating VEM into their transfusion algorithms.[64,65] Lack of consistent practices across trauma centers is likely a function of limited outcome-based studies and limited familiarity with VEM interpretation.

1.3 | Test parameters

To understand VEM guided resuscitation strategies, a basic understanding of VEM assay parameters (Table 1) and test interpretation is essential. Both TEG and

TABLE 1 Common VEM tests and associated parameters

Abbreviation	Description
TEG	Thromboelastography
rTEG	Rapid TEG
CK TEG	Citrated kaolin TEG
FF TEG	Functional fibrinogen TEG
Hep TEG	Heparinase TEG
R	Reaction time
ACT	Activated clotting time
K	Time to standard clot firmness
α	Slope between R and K (or CT and MCF)
MA	Maximal amplitude
Ly30	Lysis fraction at 30 min
EPL	Estimated percent lysis
ROTEM	Rotational thromboelastometry
EXTEM	Extrinsic ROTEM
INTEM	Intrinsic ROTEM
FIBTEM	Fibrin-based ROTEM
HEPTEM	Heparinase ROTEM
TRAPTEM	Thrombin activating peptide ROTEM
ADPTEM	ADP platelet aggregometry ROTEM
APTEM	Aprotinin ROTEM
CT	Clotting time
CA5	Clot amplitude at 5 min
CA10	Clot amplitude at 10 min
MCF	Maximal clot firmness
LI30	Lysis index (Unlysed fraction at 30 min)
LI60	Lysis index (Unlysed fraction at 60 min)
ML	Maximal lysis

ROTEM measure clot initiation, kinetics, strength, and dissolution (Table 2). Although similar in variables measured and mechanics of evaluation, side-by-side comparisons show weak or no association between the two tests[66–68] thus limiting direct comparison. Nevertheless, TEG and ROTEM tracings depict similar hemostatic functions (Figure 1) and are "substantially equivalent"[69] in terms of performance if not directly comparable. General resuscitative strategies based on abnormalities in these basic parameters are listed in Table 2.

1.4 | Logistics in trauma

Benefits of VEM-guided trauma resuscitation rely on accuracy of testing, rapid performance and availability, a strategy of iterative testing, and integration of results with clinical judgment based on the patient's injuries and hemodynamics. We have previously published a description of the key logistic elements in achieving these aims.[70] Accuracy of test results is instrument, operator, and sample dependent. Instruments should be calibrated to manufacturer specifications and operators should be trained to execute sample processing and analysis in a standardized fashion. Sample preparation begins with collection in the trauma bay. For traditional VEM, blood samples are collected in citrated tubes, sent to processing via pneumatic tube carrier, and analyzed immediately upon arrival to the laboratory. The ROTEM delta platform is less sensitive to motion than the TEG 5000 system,[71] and may therefore be available in or near the trauma bay rather than in a well-controlled laboratory. At our institution, the tracing is viewable in real time on the hospital-wide computer system via remote-viewing platform. Others have described similar measures including display of VEM results in the trauma bay.[57] Access to data on a system-wide platform is essential in the trauma patient given the potential for rapid transit between locations (eg, trauma bay, radiology, interventional radiology, operating room, and/or intensive care unit) during their initial resuscitation.[70,72] Live data availability facilitates timely decision making and the provision of a hemostatic resuscitation that is tailored to the injured patient's specific and dynamic needs.

With the advent of point-of-care devices such as the TEG 6s,[73,74] ROTEM Sigma,[75] and Hemosonics Quantra[76] and validation of the TEG 6s in trauma patients,[77] several of the above barriers to widespread VEM use may be eliminated.[78] In particular, sample preparation and transport are eliminated with point-of-care devices, and the technical challenges of sample handling and testing are greatly reduced. In addition to providing rapid data availability in the trauma bay without need for laboratory processing, such advances raise the possibility of pre-hospital viscoelastic testing. Notably, the TEG 6s has been tested in simulated environments of aeromedical evacuation[71,79,80] and ground transport.[81] Although point-of-care assays correlate relatively well with traditional VEM assays,[73,74,77,80–82] correlation is variable and environment dependent.[71,80,81] As such, further work is required to develop data-driven thresholds for point-of-care VEM guided resuscitation in the trauma bay and pre-hospital setting.

2 | RESEARCH

2.1 | Validation of VEM against CCT and patient outcomes

2.1.1 | Plasma clotting factor function

Plasma clotting factors contribute to the classically described intrinsic and extrinsic clotting cascade and are

TABLE 2 Comparison of TEG and ROTEM parameters

Hemostatic function	Primary blood component	Variable	Measurement[a]	Treatment
Clot initiation	Plasma factors	Time to first clot (2 mm deflection above baseline)	TEG: R/ACT ROTEM: CT (clotting time)	Plasma, FFP, PCC
Clot propagation	Fibrinogen	Time to standard clot firmness (from 2 mm above baseline to 20 mm above baseline)	TEG: K ROTEM: CFT (clot formation time)	Fibrinogen (cryoprecipitate)
	Fibrinogen	Rate of increase in clot	TEG: α (slope between R and K) ROTEM: α (angle of tangent at 2 mm) OR CA5 (clot amplitude at 5 min)	Fibrinogen (cryoprecipitate)
Clot strength	Platelets	Maximum strength (height of tracing)	TEG: MA (maximal amplitude) ROTEM: MCF (maximal clot firmness)	Platelets, cryoprecipitate, DDAVP
Fibrinolysis	Plasmin	Degradation of clot (% amplitude)	TEG: Ly30 ROTEM: LI (lysis index)	Tranexamic acid, ε-aminocaproic acid

Abbreviations: ACT, activated clotting time; CA5 (clot amplitude at 5 min); CFT, clot formation time; CT, clotting time; DDAVP, desmopressin; FFP, fresh frozen plasma; K, time from end of R until amplitude reaches 20 mm); LI, lysis index; Ly30, lysis fraction at 30 min; MA, maximal amplitude; MCF, maximal clot firmness; PCC, prothrombin complex concentrate; R, reaction time; ROTEM, rotational thromboelastometry; TEG, thromboelastography; α, slope between R and K (for TEG) or slope between CT and MCF (for ROTEM).
[a]Measurements and interventions described are for simple VEM limited to TEG, rapid TEG, EXTEM, and INTEM assays. Interpretation and resuscitation based off of more specific assays (eg, FIBTEM) is described in the text with details provided in Table 3 and Table 4.

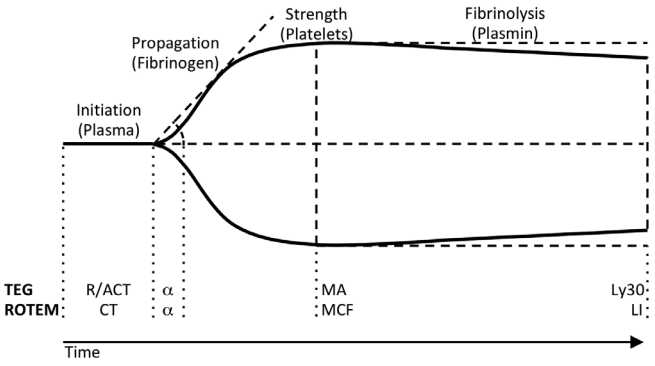
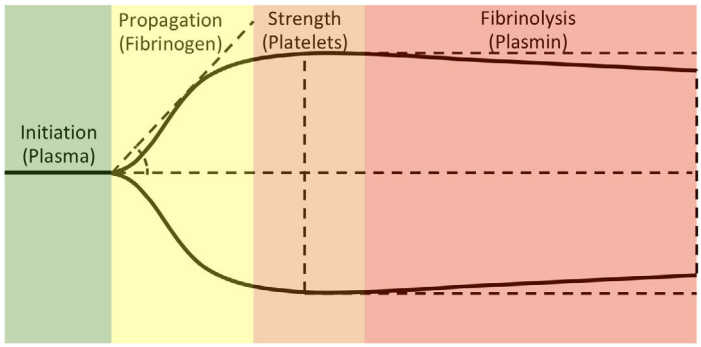


FIGURE 1 Coagulation parameters measured by VEM. Clot initiation is a function of plasma proteins and is measured as time to deviation from baseline by 2 mm in TEG (R - TEG, ACT - rTEG) and ROTEM assays (CT). Clot propagation is a function of fibrinogen deposition and is measured by the angle (α) of divergence from baseline for both TEG and ROTEM. Maximal clot strength is principally controlled by platelet function and is measured as the distance of tracing deviation from baseline for both TEG (MA) and ROTEM (MCF). Degradation of clot, or fibrinolysis, is controlled principally by plasmin and is measured as the percent decrease in amplitude at 30 minutes for TEG (Ly30) and as the percent of maximal amplitude remaining at 30 minutes for ROTEM (LI)

historically evaluated by aPTT and PT/INR, respectively. In early investigations, TIC was commonly defined as INR greater than 1.2 based on increased risk of mortality and association with increased injury severity.[7,10] Such findings led to the initial description of TIC; however, there is increasing recognition that INR likely serves as a biomarker of TIC and injury severity, but does not define the underlying pathophysiology of dysregulated hemostasis in trauma. While efforts have been made to correlate VEM parameters with CCT parameters including INR, there are overlapping, but distinct biochemical mechanisms described by these assays.[83] For example, in one study of combat casualties requiring massive transfusion, 64% had abnormal TEG values but only 10% of the same patients had PT/INR or aPTT abnormalities.[84]

Although the most recent Cochrane review did not find sufficient evidence to support TEG or ROTEM use in diagnosing TIC,[85] the practice continues to evolve based on emerging data. Furthermore, this Cochrane Review utilized CCT as the "gold standard" to which TEG/ROTEM were compared despite a lack of validation of CCT in trauma, making the approach inherently flawed. A large multinational randomized controlled trial comparing VEM-guided resuscitation against CCT-guided resuscitation (iTACTIC, ClinicalTrials.gov Identifier: NCT02593877),[86] proposed data-driven thresholds to define TIC (INR > 1.2), hypofibrinogenemia (<2.0 g/L), and thrombocytopenia (plt < 100×10^9 cells/L) for TEG and ROTEM platforms.[87] Multiple variables were found to have acceptable receiver operator characteristics to discriminate clotting factor dysfunction, hypofibriongenemia, hyperfibrinolysis, and

A



B

	Plasma (4 units)	Fibrinogen (4 g)	Platelets (1 pack)	Tranexamic acid (1 g)
TEG	rTEG MA ≥ 65 mm AND rTEG ACT > 120s	FF TEG MA < 20 mm	(rTEG MA − FF TEG MA) < 45 mm	rTEG Ly30 > 10%
ROTEM	EXTEM CA5 ≥ 40 mm AND EXTEM CT > 80 s	FIBTEM CA5 < 10 mm	(EXTEM CA5 − FIBTEM CA5) < 30 mm	LI30 < 85%
CCT	INR > 1.2 AND Fibrinogen ≥ 2 g/L	Fibrinogen < 2 g/L	Platelets < 100 x 10^9 c/L	No indication

FIGURE 2 Data-driven thresholds for additional component replacement in trauma resuscitation. A, colored-coded schematic of a normal VEM tracing indicating the four phases of clot dynamics measured by TEG and ROTEM platforms with principal biologic component responsible for the measured activity indicated. B, table adapted from Baksaas-Aasen et al with thresholds for additional component resuscitation based on VEM and CCT. Additional component quantity to be administered is indicated in parentheses. rTEG, rapid TEG; MA, maximal amplitude; ACT, activated clotting time; EXTEM, extrinsic ROTEM; CA5, clot amplitude at 5 minutes; CT, clotting time; INR, international normalized ratio; FF TEG, functional fibrinogen TEG; FIBTEM, fibrin-based ROTEM; Ly30, lysis fraction at 30 minutes; LI30, unlysed fraction at 30 minutes

thrombocytopenia (Figure 2). Increasing evidence also suggests that abnormalities early in TEG and ROTEM assays can reliably predict need for transfusion.[84,88–91] A side-by-side comparison of TEG and ROTEM in 182 severely-injured civilian trauma patients demonstrated that early changes in rTEG and EXTEM both differentiated INR cut-off of 1.2 and could predict need for increasing transfusion.[90] As part of the iTACTIC algorithm development, TEG parameters selected as thresholds for plasma administration are TEG: rTEG MA ≥65 mm AND rTEG ACT >120 seconds (ACT is the rapid TEG assay equivalent to R time) and ROTEM: EXTEM CA5 ≥ 40 mm AND EXTEM CT > 80 seconds.[87]

2.1.2 | Fibrinogen concentration and fibrinolysis

Fibrinogen conversion to fibrin is instrumental in clot formation, and low fibrinogen levels (<150 mg/dL) are frequently found in severely injured patients.[92] Relatively limited investigation has been undertaken with relation to VEM and fibrinogen levels, in part due to the ability of the gold standard Clauss method to detect hypofibrinogenemia.[93] Nevertheless, like CCTs, the Clauss method is time consuming and fibrinogen specific TEG and ROTEM assays have been developed. Functional Fibrinogen TEG (FF TEG) is a TEG assay activated by lyophilized tissue factor in the presence of platelet inhibitor Abciximab. FF TEG MA < 14.9 mm has been shown to correlate with low fibrinogen in injured adults.[94] FIBTEM is a ROTEM assay activated by tissue factor in presence of platelet inhibitor cytochalasin D; thresholds of MCF < 10 mm[94] and CA5 < 9.5 mm[95] have been used to identify fibrinogen deficiency in bleeding trauma patients. Multiple FF TEG and rTEG parameters have been shown to correlate with transfusion requirement and mortality.[96] As part of the iTACTIC algorithm development, the hypofibrinogenemia threshold identified for fibrinogen administration for TEG is FF TEG MA < 20 mm and for ROTEM is FIBTEM CA5 < 10 mm.[87]

Fibrinolysis balances fibrin deposition and clot formation in normal hemostasis. Hyperfibrinolysis occurs in up to two-thirds of severely-injured trauma patients.[97,98] Currently, the only specific recommended treatment for hyperfibrinolysis is empiric administration of the antifibrinolytic tranexamic acid (TXA)[13] within 3 hours of injury[99] based on both military and civilian studies that demonstrate reduced bleeding and overall mortality in trauma patients.[100–103] The gold standard assay of hyperfibrinolysis, euglobulin lysis time,[104,105] suffers from limited availability in standard hospital laboratories and even more pronounced time delays relative to CCTs in that results take approximately 4 hours to process.[106]

Although conventional ROTEM is relatively insensitive to detection of moderate hyperfibrinolysis in comparison to detection of plasmin-antiplasmin complexes,[98] multiple EXTEM thresholds including CA10 ≤ 10 mm, CA15 ≤ 15 mm, MCF ≤18 mm, and LI30 ≤ 71% can accurately diagnose hyperfibrinolysis when compared to euglobulin lysis.[107] Rapid TEG Ly30 cutoffs from >3%[47,108,109] to >15%[97] are able to identify post-traumatic fibrinolysis and are associated with increased risk of mortality. As part of the iTACTIC algorithm development, the hyperfibrinolysis threshold identified for additional TXA administration based on TEG is rTEG Ly30 > 10% and for ROTEM is EXTEM LI30 < 85%.[87]

Fibrinolysis shutdown (FSD), on the other end of the spectrum, is defined by Ly30 ≤ 0.8% or maximum lysis <3.5%.[110] This phenomenon is associated with poor patient outcomes in both children and adults, including death and disability.[111–114] The term likely encompasses multiple phenotypes of abnormal hemostasis: primary fibrinolysis resistance and delayed consumptive coagulopathy resulting in lack of fibrinolysis both have been proposed as mechanisms of this pathology,[115] although the existence of FSD as a unique manifestation has been challenged recently.[116] There are currently no recommended therapies beyond supportive care for FSD; however, clinical trials are underway evaluating the use of aspirin and statins in non-head injured patients to reduce lung injury and VTE complications in patients with FSD (NCT02901067).

2.1.3 | Platelet dysfunction

Platelets contribute to secondary hemostasis through thrombin generation and stabilization of the developing fibrin clot. Platelet mapping based on VEM was developed to assess platelet response to the agonists ADP and arachidonic acid (AA). Failure to respond to agonist introduction into the assay as measured by MA of clot generated is interpreted as percent inhibition of platelet receptor activity for that agonist.[117] These assays correlate well with the gold-standard assays for platelet function, impedance and light transmission aggregometry.[118,119] In severely injured trauma patients, platelet response to ADP and AA is severely impaired compared to healthy controls with ADP response inhibited 86% vs 4% and AA response inhibited 45% vs 0.5%, respectively. Poor response to ADP predicts need for platelet transfusion and poor response to AA predicts need for red blood cell transfusion.[120] As part of the iTACTIC algorithm development, the platelet dysfunction threshold for additional platelet transfusion is not based on platelet mapping but is defined based on differences in extrinsic assays and fibrin assays to eliminate the fibrin component that interacts with platelet function. For TEG assay, suggested criteria for platelet administration is defined as (rTEG MA - FF TEG MA) < 45 mm and for ROTEM is defined as (EXTEM CA5 - FIBTEM CA5) < 30 mm.[87] Overall, however, virtually every ex vivo assay of platelet function is challenged by a lack of strong clinical correlation. It is unclear if the response to agonists such as ADP or AA (whether as part of VEM or aggregometry) accurately reflects endogenous platelet (dys)function in trauma.[52,121] This is an active and important area of research in TIC.

2.2 | VEM-directed transfusion strategies

Below, we provide a summary of previously published TEG (Table 3) and ROTEM (Table 4) directed transfusion strategies. In general, smaller cohorts have been used to derive TEG,[122] rTEG,[123] citrated kaolin (CK) TEG,[124] and adult[125] and pediatric[126] EXTEM optimized thresholds for resuscitation. The remaining publications describe retrospective or prospective cohort studies, and the abundance of transfusion triggers for both TEG[39,60,70,127–136] and ROTEM[137–146] platforms are derived from expert opinion rather than data-driven thresholds. Regarding outcomes, only one randomized controlled trial comparing VEM to CCT-directed resuscitation has been published to date.[60] In this single institution study, the authors were able to demonstrate improved survival, reduced FFP transfusion, and reduced platelet transfusion in patients receiving VEM-directed resuscitation.[60] Results of the iTACTIC trial, the first multi-national randomized control trial based on data-driven transfusion triggers to assess VEM-directed resuscitation in comparison to CCT-based resuscitation, are currently pending publication.[86]

Whereas early protocols focused on basic TEG and ROTEM assays (eg, TEG, rTEG, EXTEM) and identified single variable thresholds as transfusion triggers across resuscitative components, more recent protocols have attempted to isolate specific clotting factor contributions to guide resuscitation through more complex comparisons. For example, plasma resuscitation is triggered in the iTACTIC protocol based on delayed clot initiation (rTEG ACT, EXTEM CT) but only if a high clot amplitude is achieved (rTEG MA, EXTEM CA5) suggesting normal fibrinogen deposition.[87] Although somewhat more complex, these algorithms will hopefully achieve optimization of sensitivity and specificity to accurately identify the need for component resuscitation for individual patients.

TABLE 3 TEG guided resuscitation algorithms

	Clot initiation		Clot propagation		Clot strength		Fibrinolysis		
Assay(s)	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**References**
TEG									
TEG	R > 8	Consider FFP	K > 4 α < 47	Consider Cryo	MA < 54	Consider DDAVP or Plt	Ly30 > 8%	Consider antifibrinolytic	Walsh[129]
TEG	R = 7-10 R = 11-14 R > 14	FFP 1 U (4 mL/kg) FFP 2 U (8 mL/kg) FFP 4 U (16 mL/kg)	α < 45	Cryo 0.6 U/kg	MA = 48-54 MA = 41-48 MA ≤40	DDAVP 0.3 mcg/kg Plt 5 U Plt 10 U	EPL ≥7.5%	Fibrinolytic of choice	Tapia[130]
TEG	R > 8	FFP	α < 60	Cryo after FFP	MA < 55	Plt or rFVIIa	—	—	Yao[131]
TEG	R > 10	FFP 2 U	α < 53 κ > 3	Cryo 1 U	MA < 50	Plt 1 U	Ly30 > 3%	TXA	Unruh[122]
rTEG									
rTEG	ACT >110	Consider FFP	α < 66	Consider Cryo	MA < 54	DDAVP +/− Plt	—	—	Kashuk[132]
rTEG	ACT >128 R > 1.1	FFP and pRBC	α < 56 K > 2.5	Cryo/Fbg/Plt Cryo/Fbg/FFP	MA < 55	Cryo/Fbg/Plt	Ly30 > 3%	TXA	Holcomb[133]
rTEG	ACT >110	FFP	α < 60	Cryo	MA < 50	Plt	EPL > 15%	Consider aminocaproic acid	Pezold[134]
rTEG	ACT >110	FFP 2 U	α < 63	Consider Cryo	MA < 55	Consider Plt	—	—	Sawyer[135,136]
rTEG	ACT >110	FFP 2 U	α < 60	Cryo 10 U	MA < 54	Plt 1 U	Ly30 ≥ 3%	TXA 1 g	Mauffrey[127]
rTEG	ACT >128	FFP 2 U	α < 65	Cryo 10 U	MA < 55	Plt 1 U	Ly30 ≥ 5%	TXA 1 g	Gonzalez[60]
rTEG	ACT ≥140 ACT 111-139 ACT ≤110	2 FFP, 10 cryo, 1 plt 2 FFP 2 FFP	α < 63	Cryo 10 U	MA < 55	Plt 1 U	Ly30 ≥ 3%	TXA 1 g	Gonzalez[60]
rTEG	ACT >128	FFP	α < 65	Cryo	MA < 55	Plt	Ly30 > 5%	TXA	Einersen[123]
rTEG (peds)	ACT >125	FFP 20 mL/kg	K > 3 α < 55	Cryo 1 U/10 kg	MA < 51	Plt 15 mL/kg	Ly30 > 3%	Consider TXA	Leeper[70]
CK-TEG									
CK TEG	R > 4.45	Plasma	α < 67	Cryo	MA < 60	Plt	Ly30 > 4.55%	TXA	Stettler[124]
Multiple assays									
TEG	R = 10-14 R > 14	FFP 10-20 mL/kg FFP 30 mL/kg	α < 52	FFP 20-30 mL/kg	—	—	—	—	Johansson[39]
FF TEG	—	—	—	—	MA < 14	FFP 20-30 mL/kg OR Cryo 3-5 mL/kg OR Fbg 1-2 g	—	—	

(Continues)

TABLE 3 (Continued)

	Clot initiation		Clot propagation		Clot strength		Fibrinolysis		
Assay(s)	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**References**
CK TEG	—	—	—	—	MA = 45-49 MA < 45	Plt 1 U or 5 mL/kg Plt 2 U or 10 mL/kg	Ly30 > 8% If no ↑ α or ↑ MA	TXA 1-2 g	
Hep TEG	R > 3 different from TEG	Protamine 50-100 mg OR FFP 10-20 mL/kg	—	—	—	—	—	—	
TEG	R = 10-14 R > 14	FFP 20 mL/kg FFP 30 mL/kg	—	—	MA 45-49 & FF MA > 14 MA < 45 & FF MA > 14	Plt 5 mL/kg Plt 10 mL/kg	Ly30 > 8%	TXA 1-2 g or 10-20 mg/kg	Stensballe[128]
FF TEG	—	—	MA = 7-14 MA < 7	FFP 20 mL/kg OR Cryo 3 mL/kg OR Fbg 20 mg/kg FFP 30 mL/kg OR Cryo 5 mL/kg OR Fbg 30 mg/kg	—	—	—	—	
Hep TEG	R > 2 different from TEG	Protamine 50-100 mg OR FFP 10-20 mL/kg	—	—	—	—	—	—	
rTEG	ACT >120 AND MA ≥65	Plasma 4 U	—	—	—	—	Ly30 > 10%	TXA 1 g	Baksaas-Aasen[87]
FF TEG	—	—	MA < 20	Fbg 4 g (Cryo or concentrate)	(rTEG MA) – (FF TEG MA) < 45	Plt 1 U	—	—	

Abbreviations: ACT, activated clotting time; CK TEG, citrated kaolin TEG; Cryo, cryoprecipitate; DDAVP, desmopressin; EPL, estimated percent lysis; Fbg, fibrinogen; FF TEG, functional fibrinogen TEG; FFP, fresh frozen plasma; Hep TEG, heparinase TEG; K, time to standard clot firmness; Ly30, lysis fraction at 30 min; MA, maximal amplitude; Plt, platelets; pRBC, packed red blood cells; R, reaction time; rFVIIa, recombinant factor VIIIa; rTEG, rapid TEG; TEG, thromboelastography; TXA, tranexamic acid; α, slope between R and K.

TABLE 4 ROTEM guided resuscitation algorithms

	Clot initiation		Clot propagation		Clot strength		Fibrinolysis		
Assay(s)	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**References**
EXTEM									
EXTEM	CT = 81-100 CT = 101-120 CT > 120	PCC 500-600 U PCC 1000-1200 U PCC 1500-1800 U	MCF < 50 & FIBTEM MCF < 10	Fbg to FIBTEM MCF > 10 by: ΔMCF x 6.25 mg/kg	MCF < 50 & FIBTEM MCF ≥10	Plt	"Pathologic" with normal APTEM	TXA 20 mg/kg	Durila[137]
EXTEM	CT > 78.5	Plasma	α < 64.5	Cryo	CA10 < 40.5	Plt	LI60 < 74%	TXA	Stettler[125]
EXTEM (peds)	CT > 84.5	Plasma	CA10 < 43.5	Cryo or Fbg	MCF < 64.5	Plt	—	—	Cunningham[126]
Multiple assays									
INTEM	INTEM CT > HEPTEM CT	Protamine 1-2 k U	—	—	—	—	—	—	Schochl[138–142] Schlimp[143]
EXTEM	CT = 81-100 CT = 101-120 CT > 120	PCC 500-600 U PCC 1000-1200 U PCC 1500-1800 U Alt: FFP 15-30 mL/kg	CA10 < 30	Fbg 6-8 g & TXA 15-20 mg/kg& Plt 2 U & (PCC 20-30 U/kg OR FFP 30 mL/kg)	CA10 < 40 & FIBTEM CA10 > 12	Plt	ML > 15% & APTEM ML > 15%	Consider FXIII 1250 U	
FIBTEM	—	—	CA10 ≤ 3 CA10 = 4-6	Fbg 6 g Fbg 3-4 g	—	—	—	—	
INTEM	CT > 240 (INTEM CT)/ (HEPTEM CT) > 1.0	FFP 10-15 mL/kg OR PCC 20 IU/kg Protamine 25-50 mg	—	—	—	—	—	—	Tanaka[144]
EXTEM	CT > 100	FFP 10-15 mL/kg OR PCC 20 IU/kg	MCF < 45 & FIBTEM MCF < 10 MCF > 45 & FIBTEM MCF < 10	Cryo/Fbg + Plt 1 U Cryo/Fbg	MCF < 35 & FIBTEM MCF ≥10 MCF = 35-45 & FIBTEM MCF ≥10	Plt 1-2 U Plt 1 U	-	-	
FIBTEM	—	—	CA10 < 8 CA10 < 5	Cryo 10 U OR Fbg 2 g Cryo 20 U OR Fbg 4 g	—	—	"Fibrinolysis pattern"	TXA 1-2 g OR aminocaproic acid 5-10 g	
INTEM	CT 200-240 CT > 240	FFP 20 mL/kg FFP 30 mL/kg	—	—	—	—	—		Stensballe[128]
EXTEM	CT 80-100 CT > 100	FFP 20 mL/kg FFP 30 mL/kg	—	—	CA10 35-42 & FIBTEM CA10 ≥ 10 OR MCF < 50 & FIBTEM MCF ≥10 CA10 < 35 & FIBTEM CA10 ≥ 10	Plt 5 mL/kg Plt 10 mL/kg	LI30 < 94%	TXA 1-2 g or 10-20 mg	
FIBTEM	—	—	MCF = 6-9 MCF < 6	FFP 20 mL/kg OR Cryo 3 mL/kg OR Fbg 20 mg/kg FFP 30 mL/kg OR Cryo 5 mL/kg OR Fbg 30 mg/kg	—	—	—	—	

(Continues)

TABLE 4 (Continued)

	Clot initiation		Clot propagation		Clot strength		Fibrinolysis		
Assay(s)	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**Threshold**	**Treatment**	**References**
HEPTEM	(INTEM CT)/ (HEPTEM CT) > 1.25	Protamine 50-100 mg OR FFP 10-20 mL/kg	—	—	—	—	—	—	
EXTEM (peds)	CT > 90 OR INR > 1.5	PCC 25 U/kg OR FFP	—	—	—	—	—	—	Deng[145]
FIBTEM (peds)	—	—	MCF < 7	Fbg 25-50 mg/kg	MCF ≤10-12 OR Plt < 50 × 10^9 c/L	Plt	—	—	
INTEM	CT > 240 & (INTEM CT/ HEPTEM CT) ≥ 1.25 OR CT > 240 & (INTEM CT/ HEPTEM CT) < 1.25	Protamine 0.5 mg/kg FFP 10 mL/kg	—	—	—	—	—	—	Gorlinger[146]
EXTEM	CT > 80 & FIBTEM A5 ≥ 9	4F-PCC 15-25 IU/kg OR FFP 10-15 mL/kg	CA5 < 35 & FIBTEM CA5 < 9	Fbg or Cryo To target FIBTEM A5 ≥ 12	CA5 < 35 & FIBTEM CA5 ≥ 9 OR CA5 < 35 & TRAPTEM <50 or ADPTEM <40	Plt 5-10 mL/kg	CA5 < 35	TXA 15-25 mg/kg	
FIBTEM	—	—	—	—	—	—	CT > 600	TXA 15-25 mg/kg	
Undefined	—	—	—	—	—	—	ML ≥5%	TXA 15-25 mg/kg	
EXTEM	CA5 ≥ 40 & CT > 80	Plasma 4 U	—	—	—	—	LI30 < 85%	TXA 1 g	Baksaas-Aasen[87]
FIBTEM	—	—	CA5 < 10	Fbg 4 g (Cryo or concentrate)	(EXTEM CA5) - (FIBTEM CA5) < 30	Plt 1 U	—	—	

Abbreviations: ADPTEM, ADP platelet aggregometry ROTEM; Alt, alternatively; APTEM, aprotinin ROTEM; CA10, clot amplitude at 10 min; CA5, clot amplitude at 5 min; Cryo, cryoprecipitate; CT, clotting time; EXTEM, extrinsic ROTEM; Fbg, fibrinogen; FFP, fresh frozen plasma; FIBTEM, fibrin-based ROTEM; FXIII, factor XIII; HEPTEM, heparinase ROTEM; INTEM, intrinsic ROTEM; IU, international units; LI30, unlysed fraction at 30 min; LI60, unlysed fraction at 60 min; MCF, maximal clot firmness; ML, maximal lysis; PCC, prothrombin complex concentrate; Plt, platelets; TRAPTEM, thrombin activating peptide ROTEM; TXA, tranexamic acid; α, slope between CT and MCF.

2.3 | Hypercoagulability

Thromboembolic events are common in injured adults with incidence up to 58% depending upon method of detection and study design.[147–150] In line with this concern, application of VEM platforms to identify hypercoagulable trauma patients has been undertaken.[108,151–155] Elevated TEG MA on admission has been correlated with increased incidence of pulmonary embolism in a retrospective observational study.[151] TEG MA greater than 65 mm was found to independently predict pulmonary embolism with direct correlation between further increases in MA and risk of such an event in a prospective study,[152] and similar correlation has been noted prospectively for elevated TEG MA and risk of venous thromboembolism (VTE) and pulmonary embolism (PE) in extremity trauma.[153] The shear elastic modulus (G) is indicative of clot strength, and elevations in this parameter have also been correlated with increased thromboembolic events in blunt abdominal trauma.[154] These data are generally limited by their observational nature but support the idea that VEM parameters may predict clinically significant sequelae of hypercoagulability.

In injured children, risk of VTE in general is substantially lower than in adults, though high risk populations include those with traumatic brain injury and bimodal age distribution (age < 3 years and age > 13 years).[108,155] A TEG MA ≥ 65 mm is found in approximately one third of all pediatric trauma patients, though an association of admission TEG MA with future VTE has not been established. In contrast, admission FSD (LY30 ≤ 0.8%) is common and has been associated with subsequent development of deep vein thrombosis.[114]

Based on these findings, thromboprophylaxis is strongly recommended in adult trauma patients; however, VEM measures of hypercoagulability remain abnormal in spite of such treatment.[156] These findings beg the question of whether current thromboprophylaxis in trauma is adequate. Alternatively, abnormal VEM may be of limited clinical utility in assessing thromboprophylaxis efficacy. Future studies are needed to investigate whether VEM-directed thromboprophylaxis protocols may be superior to, or capable of adequately monitoring, current standard dose regimens for VTE prevention.

2.4 | Role in patients taking antiplatelet/anticoagulation

A major challenge in caring for trauma patients is frequent lack of past medical history including knowledge of antiplatelet and/or anticoagulant therapy history. VEM, including TEG ADP and AA response platelet mapping, has been investigated as a means of evaluating pre-injury antiplatelet administration. In these studies, specificity is poor,[157] the range of values identified as indicative of control vs drug groups overlap,[158] source of platelet dysfunction is difficult to differentiate from trauma-mediated dysfunction,[159] and performance relative to alternatives such as aggregometry is poor.[160,161] Thus, no evidence is available to support TEG or ROTEM use in detecting antiplatelet therapy at present.[162] Detection of warfarin and novel oral anticoagulants (NOACs) is similarly unreliable, due to the fact that the test is run with added reagents that mask the presence of an anticoagulant.[163–165] Titrated NOAC added to blood samples *ex vivo* can be used to develop a standard curve for VEM assays,[166] and in other studies, well defined cohorts of patients taking a single drug had blood collected at a prescribed interval post-administration with effective differentiation of drug vs placebo.[167–169] Unfortunately, these experiments are limited by the homogeneity of samples assessed and development of real-world thresholds in the setting of trauma with variable renal function and unknown dose administration time, agent, etc. prevents robust discrimination of presence of NOACs. Thus, direct measurement of drug concentrations remains the gold standard test for detection of anticoagulants, and application of VEM in this clinical context is not recommended.[170,171]

2.5 | Pediatric trauma

Injury represents a growing public health epidemic and is the number one cause of mortality in young adults and children over the age of one. Children who are undertreated and undertriaged have worse outcomes compared to those who receive timely and appropriate care after injury.[172,173] As in adults, resuscitative strategies in children emphasize bleeding cessation, damage control hemostatic resuscitation and prevention/mitigation of TIC. Importantly, permissive hypotension is not a recommended strategy in pediatric trauma. Children have the physiologic reserve to maintain normotension to the verge of circulatory collapse; hypotension is a sign that a child is in extremis and should be treated with aggressive resuscitation.

As is true for many fields of research, data on use of VEM in pediatric trauma is limited in comparison to adults.[174] Although significant concordance in findings has been published as discussed throughout this review, pediatric trauma differs substantially from adult trauma in many respects. Crucially, the incidence of traumatic brain injury is high, hemorrhagic shock and penetrating mechanism is less prevalent, and child abuse represents a

unique and complex mechanism that includes anoxic injury, blunt force, shearing force from shaking, and spinal cord injury from whiplash.[175] Although overlapping mechanisms of TIC may be at play,[46,47,114,176,177] normal values for laboratory studies developed in adults may not align exactly with reference range values amongst pediatric controls.[176] Nevertheless, dysregulation of clot strength, fibrinolysis, and clotting factors have been associated with increased mortality, increased thromboembolic events, and increased transfusion requirements/mortality, respectively.[178]

Few protocols for VEM-directed resuscitation have been developed specifically for pediatric patients.[70,126,145] Many pediatric trauma centers rely on adult ranges or do not utilize VEM-guided resuscitation due to lack of pediatric-specific data, lack of familiarity with interpretation of tests and/or lack of appropriate laboratory resources to run VEM assays. Nevertheless, decreased blood product administration and more rapid recovery of coagulopathic profiles in pediatric patients managed with a ROTEM-directed transfusion strategy has been demonstrated.[145] We are not aware of any ongoing clinical trials investigating use of VEM in pediatric populations with exception of monitoring outcomes in treatment with fibrinogen vs cryoprecipitate (FEISTY Jnr NCT03508141). iTACTIC inclusion criteria, similar to many studies surrounding TIC/VEM, are limited to individuals 16 years or older.

3 | CONCLUSION

3.1 | Pitfalls

Caution must be exercised in depending upon VEM for trauma resuscitation without appropriate context. The clinician should recall that these assays are *ex vivo* analyses of dynamic *in vivo* systems. TEG and ROTEM assays are limited to assessment of secondary hemostasis only, and neither provides information on vascular or primary hemostatic mechanisms. Failure of VEM to identify primary disorders of hemostasis, for example von Willebrand disorder, highlights this limitation.[179] Original descriptions of trauma's "bloody vicious cycle" identified three components to the lethal triad: coagulopathy, hypothermia, and acidosis.[180] VEM assays are conducted under ideal laboratory settings in the absence of these factors, which are commonly seen after injury and may contribute to vastly different coagulation profiles in the patient as compared with the test tube.

As discussed above, pharmacologic disruptions of coagulation including antiplatelet and anticoagulant therapies cannot be accurately evaluated by VEM.[159,162–165] An aging trauma patient population presents with diverse and often unknown exposures including these and other pharmacologic modulators. Further, ROTEM measurements may be affected by ethanol[181] and TEG results may not correlate reliably with CCTs or patient outcomes in the intoxicated trauma patient,[182,183] thus significant care must be taken when interpreting VEM in intoxicated trauma patients. Effects of additional recreational/medical therapies are as yet unknown.

In addition to environmental factors and ethanol, sex and age also contribute to discrepancies in coagulation profiles. Recent work has demonstrated a mortality impact of sex differences in coagulation profiles with females demonstrating a more hypercoagulable profile and survival benefit in the setting of depressed clot strength.[184] As discussed above, investigations of VEM in pediatric patients are relatively limited in comparison to adults; extrapolating findings from adult studies to the care of pediatric trauma patients should be done with caution. At the other extreme of age, traumatic coagulopathy may be less frequent in elderly patients.[185] Elderly patients present with more comorbid conditions and higher incidence of polypharmacy, and clinical indicators that may prompt resuscitation in younger patients are frequently altered in geriatric trauma patients.[186] These differences may alter resuscitation in general, and must be considered carefully given that baseline VEM parameters may be different in healthy elderly volunteers relative to younger adult controls.[187]

3.2 | Benefits

In spite of these limitations, VEM assays have a growing role in the care of the trauma patient. VEM assays have utility in prognostication, as any abnormal coagulation profile, whether hypocoagulable, hypercoagulable, or mixed, has been associated consistently with increased mortality and morbidity in trauma patients.[109] Regarding resuscitation practice, the singular prospective randomized control trial published to date demonstrated improved mortality when resuscitation was guided by VEM as compared to CCT.[60] This study was limited by constraints on turn-around time of CCTs, and others have argued that clinicians unconstrained by the limits of clinical trials perform equally effectively to those guided by VEM.[188] Meta-analyses have come to similar conclusions, but have also demonstrated decreased transfusion of unnecessary products.[85,189] These changes are likely dependent upon local practice as other studies have demonstrated increased blood product administration[133]; however, standardization of thresholds[86,87] may alter these findings. Cost-effectiveness[190] and shorter length of stay[191] have also been demonstrated.

3.3 | Future directions

VEM assays appear to be particularly adept in differentiating injury-related fibrinolysis phenotypes and directing treatment related to these differences.[93,192,193] ROTEM can detect treatment with and response to fibrinogen, plasma, platelets, and TXA in critically injured trauma patients.[194] Recent work suggests that clinically-relevant parameters may be estimated earlier in the course of TEG assay processing thereby facilitating a more comprehensive understanding of resuscitation needs.[195] Device development to improve reliability, repeatability, and ease of data generation continues to improve potential for widespread application.[77] As point of care testing develops and utilization becomes more widespread, our understanding of application to trauma resuscitation is likely to grow. Such technology may facilitate earlier guidance of hemostatic resuscitation including during patient transport and in austere environments such as combat zones that would otherwise be unable to achieve the necessary laboratory settings for accurate VEM.

Currently, 12 clinical trials are recruiting or pending initiation for use of VEM in trauma. These tests span the spectrum of interventions from guidance of resuscitation using ROTEM in TBI (THROMBIN NCT03616808) to comparison of devices (ROTCLOT NCT04107818, VISCOTRAUMA NCT03380676, STAT NCT02901067, STAR NCT03780894) to identification of physiologic derangements (ROTATe IT NCT03765866, NCT03730 415, TrICI NCT03128658) and others (FEISTY Jnr NCT03508141, NCT04165538, PRETIC NCT03780894). These trials will contribute to the growing body of literature advancing the field of hemostatic resuscitation in critically injured patients.

Concepts in trauma resuscitation are rapidly evolving, and VEM technologies are poised to facilitate change. From the direction of component provision in a dynamic hemostatic resuscitation to the broader understanding of patient physiology after injury, VEM provides rapid and detailed information to guide and improve care of the trauma patient.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

Related to the content of this manuscript, MDN has received research support from Haemonetics and Instrument Laboratories and has received an honorarium from Haemonetics for a speaking engagement. Unrelated to the content of this manuscript, MDN has received research support from Janssen Pharmaceuticals and Noveome. He has served as a consultant to Janssen and CSL Behring. He serves on the Scientific Advisory Board of Haima Therapeutics. ACS and CML declare no conflict of interest related to the publication of this manuscript.

ORCID

Andrew C. Sayce https://orcid.org/0000-0003-1108-3895
Matthew D. Neal https://orcid.org/0000-0001-8931-6236
Christine M. Leeper https://orcid.org/0000-0002-8561-8760

REFERENCES

1. Collaborators GBD 2017 Causes of Death. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2018;392(10159):1736–1788.
2. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Sci Am. 1983;249(2):28–35.
3. Valdez C, Sarani B, Young H, Amdur R, Dunne J, Chawla LS. Timing of death after traumatic injury–a contemporary assessment of the temporal distribution of death. J Surg Res. 2016; 200(2):604–609.
4. Gunst M, Ghaemmaghami V, Gruszecki A, Urban J, Frankel H, Shafi S. Changing epidemiology of trauma deaths leads to a bimodal distribution. Proc (Bayl Univ Med Cent). 2010;23(4):349–354.
5. Cole E, Weaver A, Gall L, et al. A decade of damage control resuscitation: new transfusion practice, new survivors, new directions. Ann Surg. 2019; [Publish Ahead of Print]. https://doi.org/10.1097/SLA.0000000000003657.
6. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. J Trauma. 2006;60 (6 Suppl):S3–S11.
7. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54(6):1127–1130.
8. Frith D, Davenport R, Brohi K. Acute traumatic coagulopathy. Curr Opin Anaesthesiol. 2012;25(2):229–234.
9. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care. 2007;13(6):680–685.
10. Frith D, Goslings JC, Gaarder C, et al. Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations. J Thromb Haemost. 2010;8(9):1919–1925.
11. 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.
12. Wafaisade A, Lefering R, Bouillon B, et al. Epidemiology and risk factors of sepsis after multiple trauma: an analysis of 29,829 patients from the Trauma Registry of the German Society for Trauma Surgery. Crit Care Med. 2011;39(4): 621–628.
13. Harris T, Davenport R, Mak M, Brohi K. The evolving science of trauma resuscitation. Emerg Med Clin North Am. 2018;36 (1):85–106.

14. Duke MD, Guidry C, Guice J, et al. Restrictive fluid resuscitation in combination with damage control resuscitation: time for adaptation. J Trauma Acute Care Surg. 2012;73(3): 674–678.
15. Schreiber MA, Meier EN, Tisherman SA, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg. 2015;78(4):687–697.
16. Beuran M, Negoi I, Paun S, Runcanu A, Gaspar B. [History of trauma care]. Chirurgia (Bucur). 2011;106(5):573–580.
17. Bickell WH, Wall MJJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med. 1994;331(17):1105–1109.
18. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma. 2007;62(2):307–310.
19. Brown JB, Cohen MJ, Minei JP, et al. Debunking the survival bias myth: Characterization of mortality during the initial 24 hours for patients requiring massive transfusion. J Trauma Acute Care Surg. 2012;73(2):358–364; discussion 364.
20. Johansson PI, Stensballe J. Hemostatic resuscitation for massive bleeding: the paradigm of plasma and platelets—a review of the current literature. Transfusion. 2010;50(3):701–710.
21. Holcomb JB, Zarzabal LA, Michalek JE, et al. Increased platelet: RBC ratios are associated with improved survival after massive transfusion. J Trauma. 2011;71(2 Suppl 3):S318–S328.
22. Bhangu A, Nepogodiev D, Doughty H, Bowley DM. Meta-analysis of plasma to red blood cell ratios and mortality in massive blood transfusions for trauma. Injury. 2013;44(12): 1693–1699.
23. Anto VP, Guyette FX, Brown J, et al. Severity of hemorrhage and the survival benefit associated with plasma: results from a randomized prehospital plasma trial. J Trauma Acute Care Surg. 2020;88(1):141–147.
24. Maw G, Furyk C. Pediatric massive transfusion: a systematic review. Pediatr Emerg Care. 2018;34(8):594–598.
25. Chidester SJ, Williams N, Wang W, Groner JI. A pediatric massive transfusion protocol. J Trauma Acute Care Surg. 2012;73(5):1273–1277.
26. Hendrickson JE, Shaz BH, Pereira G, et al. Implementation of a pediatric trauma massive transfusion protocol: one institution's experience. Transfusion. 2012;52(6):1228–1236.
27. Nosanov L, Inaba K, Okoye O, et al. The impact of blood product ratios in massively transfused pediatric trauma patients. Am J Surg. 2013;206(5):655–660.
28. Edwards MJ, Lustik MB, Clark ME, Creamer KM, Tuggle D. The effects of balanced blood component resuscitation and crystalloid administration in pediatric trauma patients requiring transfusion in Afghanistan and Iraq 2002 to 2012. J Trauma Acute Care Surg. 2015;78(2):330–335.
29. 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):471–482.
30. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: Fifth edition. Crit Care. 2019;23(1):98.
31. Martinaud C, Tiberghien P, Begue S, et al. Rational and design of the T-STORHM study: a prospective randomized trial comparing fresh whole blood to blood components for acutely bleeding trauma patients. Transfus Clin Biol. 2019;26 (4):198–201.
32. Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. J Trauma Acute Care Surg. 2016;81(1):21–26.
33. Pivalizza EG, Stephens CT, Sridhar S, et al. Whole blood for resuscitation in adult civilian trauma in 2017: a narrative review. Anesth Analg. 2018;127(1):157–162.
34. Leeper CM, Yazer MH, Cladis FP, Saladino R, Triulzi DJ, Gaines BA. Use of uncrossmatched cold-stored whole blood in injured children with hemorrhagic shock. JAMA Pediatr. 2018;172(5):491–492.
35. Guyette FX, Sperry JL, Peitzman AB, et al. Prehospital blood product and crystalloid resuscitation in the severely injured patient: a secondary analysis of the prehospital air medical plasma trial. Ann Surg. 2019; [Publish Ahead of Print]. https://doi.org/10.1097/SLA.0000000000003324.
36. Sperry JL, Guyette FX, Brown JB, et al. Prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock. N Engl J Med. 2018;379(4):315–326.
37. Pusateri AE, Moore EE, Moore HB, et al. Association of Prehospital Plasma Transfusion with Survival in trauma patients with hemorrhagic shock when transport times are longer than 20 minutes: a post hoc analysis of the PAMPer and COMBAT clinical trials. JAMA Surg. 2020;155(2):e195085.
38. Shackelford SA, Del Junco DJ, Powell-Dunford N, et al. Association of prehospital blood product transfusion during medical evacuation of combat casualties in Afghanistan with acute and 30-day survival. JAMA. 2017;318(16):1581–1591.
39. Johansson PI, Sorensen AM, Larsen CF, et al. Low hemorrhage-related mortality in trauma patients in a level I trauma center employing transfusion packages and early thromboelastography-directed hemostatic resuscitation with plasma and platelets. Transfusion. 2013;53(12):3088–3099.
40. Johansson PI, Stensballe J, Oliveri R, Wade CE, Ostrowski SR, Holcomb JB. How I treat patients with massive hemorrhage. Blood. 2014;124(20):3052–3058.
41. Abdelfattah K, Cripps MW. Thromboelastography and rotational thromboelastometry use in trauma. Int J Surg. 2016;33 (Pt B):196–201.
42. Whittaker B, Christiaans SC, Altice JL, et al. Early coagulopathy is an independent predictor of mortality in children after severe trauma. Shock. 2013;39(5):421–426.
43. Patregnani JT, Borgman MA, Maegele M, Wade CE, Blackbourne LH, Spinella PC. Coagulopathy and shock on admission is associated with mortality for children with traumatic injuries at combat support hospitals. Pediatr Crit Care Med. 2012;13(3):273–277.
44. Hollingworth W, Vavilala MS, Jarvik JG, et al. The use of repeated head computed tomography in pediatric blunt head trauma: factors predicting new and worsening brain injury. Pediatr Crit Care Med. 2007;8(4):348–356; CEU quiz 357.
45. Christiaans SC, Duhachek-Stapelman AL, Russell RT, Lisco SJ, Kerby JD, Pittet J-F. Coagulopathy after severe pediatric trauma. Shock. 2014;41(6):476–490.
46. Hendrickson JE, Shaz BH, Pereira G, et al. Coagulopathy is prevalent and associated with adverse outcomes in

transfused pediatric trauma patients. J Pediatr. 2012;160(2): 204–209.e3.
47. Leeper CM, Kutcher M, Nasr I, et al. Acute traumatic coagulopathy in a critically injured pediatric population: definition, trend over time, and outcomes. J Trauma Acute Care Surg. 2016;81(1):34–41.
48. Chiaretti A, Pezzotti P, Mestrovic J, et al. The influence of hemocoagulative disorders on the outcome of children with head injury. Pediatr Neurosurg. 2001;34(3):131–137.
49. Reed CR, Williamson H, Vatsaas C, et al. Higher mortality in pediatric and adult trauma patients with traumatic coagulopathy, using age-adjusted diagnostic criteria. Surgery. 2019;165(6):1108–1115.
50. Bouzat P, Ageron F-X, Charbit J, et al. Modelling the association between fibrinogen concentration on admission and mortality in patients with massive transfusion after severe trauma: an analysis of a large regional database. Scand J Trauma Resusc Emerg Med. 2018;26(1):55.
51. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. Injury. 2017;48(5):1074–1081.
52. Vulliamy P, Kornblith LZ, Kutcher ME, Cohen MJ, Brohi K, Neal MD. Alterations in platelet behavior after major trauma: adaptive or maladaptive? Platelets. 2020;1–10. https://doi.org/10.1080/09537104.2020.1718633.
53. David J-S, Durand M, Levrat A, et al. Correlation between laboratory coagulation testing and thromboelastometry is modified during management of trauma patients. J Trauma Acute Care Surg. 2016;81(2):319–327.
54. van den Besselaar AM, Evatt BL, Brogan DR, Triplett DA. Proficiency testing and standardization of prothrombin time: effect of thromboplastin, instrumentation, and plasma. Am J Clin Pathol. 1984;82(6):688–699.
55. van den Besselaar AM. Standardization of the prothrombin time in oral anticoagulant control. Haemostasis. 1985;15(4): 271–277.
56. Loeliger EA, van den Besselaar AM, Lewis SM. Reliability and clinical impact of the normalization of the prothrombin times in oral anticoagulant control. Thromb Haemost. 1985;53(1): 148–154.
57. 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):407–417.
58. David J-S, Levrat A, Inaba K, et al. Utility of a point-of-care device for rapid determination of prothrombin time in trauma patients: a preliminary study. J Trauma Acute Care Surg. 2012;72(3):703–707.
59. Gonzalez E, Pieracci FM, Moore EE, Kashuk JL. Coagulation abnormalities in the trauma patient: the role of point-of-care thromboelastography. Semin Thromb Hemost. 2010;36(7): 723–737.
60. 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): 1051–1059.
61. Avikainen V. Coagulation disorders in severely and critically injured patients. Ann Chir Gynaecol. 1977;66(6): 269–277.
62. Kaufmann CR, Dwyer KM, Crews JD, Dols SJ, Trask AL. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma. 1997;42(4):712–716.
63. American College of Surgeons Committee on Trauma. Advanced Trauma Life Support (ATLS) Student Course Manual. 10th ed. Chicago, IL: American College of Surgeons; 2018.
64. Etchill E, Sperry J, Zuckerbraun B, et al. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. Transfusion. 2016;56(10):2478–2486.
65. Camazine MN, Hemmila MR, Leonard JC, et al. Massive transfusion policies at trauma centers participating in the American College of Surgeons trauma quality improvement program. J Trauma Acute Care Surg. 2015;78(6 Suppl 1): S48–S53.
66. Sankarankutty A, Nascimento B, Teodoro da Luz L, Rizoli S. TEG(R) and ROTEM(R) in trauma: similar test but different results? World J Emerg Surg. 2012;7(Suppl 1):S3.
67. Hagemo JS, Naess PA, Johansson P, et al. Evaluation of TEG ((R)) and RoTEM((R)) inter-changeability in trauma patients. Injury. 2013;44(5):600–605.
68. Rizoli S, Min A, Sanchez AP, et al. In trauma, conventional ROTEM and TEG results are not interchangeable but are similar in clinical applicability. Mil Med. 2016;181(5 Suppl): 117–126.
69. Friemert V-J. ROTEM delta Thromboelastometry System 510 (k) Submission. Munich, Germany: Pentapharm GmbH; 2010.
70. Leeper CM, Gaines BA. Viscoelastic hemostatic assays in the management of the pediatric trauma patient. Semin Pediatr Surg. 2017;26(1):8–13.
71. Meledeo MA, Peltier GC, McIntosh CS, Voelker CR, Bynum JA, Cap AP. Functional stability of the TEG 6s hemostasis analyzer under stress. J Trauma Acute Care Surg. 2018; 84(6S Suppl 1):S83–S88.
72. Gonzalez E, Moore EE, Moore HB. Management of trauma-induced coagulopathy with thrombelastography. Crit Care Clin. 2017;33(1):119–134.
73. Gurbel PA, Bliden KP, Tantry US, et al. First report of the point-of-care TEG: a technical validation study of the TEG-6S system. Platelets. 2016;27(7):642–649.
74. Lloyd-Donald P, Churilov L, Zia F, et al. Assessment of agreement and interchangeability between the TEG5000 and TEG6S thromboelastography haemostasis analysers: a prospective validation study. BMC Anesthesiol. 2019;19(1):45.
75. Schenk B, Görlinger K, Treml B, et al. A comparison of the new ROTEM(®) sigma with its predecessor, the ROTEMdelta. Anaesthesia. 2019;74(3):348–356.
76. Ferrante EA, Blasier KR, Givens TB, Lloyd CA, Fischer TJ, Viola F. A novel device for the evaluation of hemostatic function in critical care settings. Anesth Analg. 2016;123(6): 1372–1379.
77. Neal MD, Moore EE, Walsh M, et al. A comparison between the TEG 6s and TEG 5000 analyzers to assess coagulation in trauma patients. J Trauma Acute Care Surg. 2020;88(2): 279–285.
78. Morton S, Galea J, Uprichard J, Hudson A. The practicalities and barriers of using TEG6s in code red traumas: an observational study in one London major trauma centre. CJEM. 2019; 21(3):361–364.

79. Scott R, Burns B, Ware S, Oud F, Miller M. The reliability of thromboelastography in a simulated rotary wing environment. Emerg Med J. 2018;35(12):739–742.
80. Gill M. The TEG(R)6s on shaky ground? A novel assessment of the TEG(R)6s performance under a challenging condition. J Extra Corpor Technol. 2017;49(1):26–29.
81. Roberts TR, Jones JA, Choi J-H, et al. Thromboelastography on-the-go: evaluation of the TEG 6s device during ground and high-altitude Aeromedical Evacuation with extracorporeal life support. J Trauma Acute Care Surg. 2019;87(1S Suppl 1):S119–S127.
82. Wong Q, Byrne KP, Robinson SC. Clinical agreement and interchangeability of TEG5000 and TEG6s during cardiac surgery. Anaesth Intensive Care. 2020;48(1):43–52.
83. Sumislawski JJ, Christie SA, Kornblith LZ, et al. Discrepancies between conventional and viscoelastic assays in identifying trauma-induced coagulopathy. Am J Surg. 2019;217(6):1037–1041.
84. Doran CM, Woolley T, Midwinter MJ. Feasibility of using rotational thromboelastometry to assess coagulation status of combat casualties in a deployed setting. J Trauma. 2010;69 (Suppl 1):S40–S48.
85. 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.
86. Gaarder C, Brohi K. Implementing Treatment Algorithms for the Correction of Trauma Induced Coagulopathy (iTACTIC) NCT02593877 [Internet]. ClinicalTrials.gov. 2018. https://clinicaltrials.gov/ct2/show/NCT02593877. Accessed February 29, 2020.
87. Baksaas-Aasen K, Van Dieren S, Balvers K, et al. Data-driven development of ROTEM and TEG algorithms for the management of trauma hemorrhage: a prospective observational multicenter study. Ann Surg. 2019;270(6):1178–1185.
88. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med. 2011;39(12):2652–2658.
89. Hagemo JS, Christiaans SC, Stanworth SJ, et al. Detection of acute traumatic coagulopathy and massive transfusion requirements by means of rotational thromboelastometry: an international prospective validation study. Crit Care. 2015;19:97.
90. Meyer ASP, Meyer MAS, Sorensen AM, et al. Thrombelastography and rotational thromboelastometry early amplitudes in 182 trauma patients with clinical suspicion of severe injury. J Trauma Acute Care Surg. 2014;76(3):682–690.
91. Moore HB, Moore EE, Chin TL, et al. Activated clotting time of thrombelastography (T-ACT) predicts early postinjury blood component transfusion beyond plasma. Surgery. 2014;156(3):564–569.
92. Chambers LA, Chow SJ, Shaffer LET. Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. Am J Clin Pathol. 2011;136(3):364–370.
93. Peng HT, Nascimento B, Beckett A. Thromboelastography and thromboelastometry in assessment of fibrinogen deficiency and prediction for transfusion requirement: a descriptive review. Biomed Res Int. 2018;2018:7020539.
94. Meyer MAS, Ostrowski SR, Sorensen AM, et al. Fibrinogen in trauma, an evaluation of thrombelastography and rotational thromboelastometry fibrinogen assays. J Surg Res. 2015;194 (2):581–590.
95. 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(7):1342–1351.
96. Laursen TH, Meyer MAS, Meyer ASP, et al. Thrombelastography early amplitudes in bleeding and coagulopathic trauma patients: results from a multicenter study. J Trauma Acute Care Surg. 2018;84(2):334–341.
97. 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.
98. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. J Thromb Haemost. 2013;11(2):307–314.
99. Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron F-X, Roberts I. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet (London, England). 2018;391(10116):125–132.
100. 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 (London, England). 2010;376(9734):23–32.
101. Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. Ann Surg. 2015;261(2):390–394.
102. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg. 2012;147(2):113–119.
103. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II study. JAMA Surg. 2013;148(3):218–225.
104. Macfarlane RG, Biggs R. Fibrinolysis; its mechanism and significance. Blood. 1948;3(10):1167–1187.
105. Kowalski E, Kopec M, Niewiarowski S. An evaluation of the euglobulin method for the determination of fibrinolysis. J Clin Pathol. 1959;12(3):215–218.
106. Smith AA, Jacobson LJ, Miller BI, Hathaway WE, Manco-Johnson MJ. A new euglobulin clot lysis assay for global fibrinolysis. Thromb Res. 2003;112(5–6):329–337.
107. 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):792–797.
108. Liras IN, Rahbar E, Harting MT, Holcomb JB, Cotton BA. When children become adults and adults become most hypercoagulable after trauma: an assessment of admission hypercoagulability by rapid thrombelastography and venous thromboembolic risk. J Trauma Acute Care Surg. 2016;80(5):778–782.
109. Moore HB, Moore EE, Liras IN, et al. Targeting resuscitation to normalization of coagulating status: hyper and

hypocoagulability after severe injury are both associated with increased mortality. Am J Surg. 2017;214(6):1041–1045.
110. Gomez-Builes JC, Acuna SA, Nascimento B, Madotto F, Rizoli SB. Harmful or physiologic: diagnosing fibrinolysis shutdown in a trauma cohort with rotational Thromboelastometry. Anesth Analg. 2018;127(4):840–849.
111. Meizoso JP, Karcutskie CA, Ray JJ, Namias N, Schulman CI, Proctor KG. Persistent fibrinolysis shutdown is associated with increased mortality in severely injured trauma patients. J Am Coll Surg. 2017;224(4):575–582.
112. Leeper CM, Neal MD, McKenna CJ, Gaines BA. Trending fibrinolytic dysregulation: fibrinolysis shutdown in the days after injury is associated with poor outcome in severely injured children. Ann Surg. 2017;266(3):508–515.
113. 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):811–817; discussion 817.
114. Leeper CM, Neal MD, McKenna C, Sperry JL, Gaines BA. Abnormalities in fibrinolysis at the time of admission are associated with deep vein thrombosis, mortality, and disability in a pediatric trauma population. J Trauma Acute Care Surg. 2017;82(1):27–34.
115. Moore HB, Moore EE, Neal MD, et al. Fibrinolysis shutdown in trauma: historical review and clinical implications. Anesth Analg. 2019;129(3):762–773.
116. Gall LS, Vulliamy P, Gillespie S, Jones, TF, Pierre RSJ, Breukers SE, Gaarder C, Juffermans N, Maegele M, Stensballe J, Johansson PI, Davenport RA, Brohi K. Targeted Action for Curing Trauma-Induced Coagulopathy (TACTIC). The S100A10 pathway mediates an occult hyperfibrinolytic subtype in trauma patients. Ann Surg. 2019;269(6):1184–1191.
117. Tantry US, Bliden KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. J Am Coll Cardiol. 2005;46(9):1705–1709.
118. Velik-Salchner C, Maier S, Innerhofer P, et al. An assessment of cardiopulmonary bypass-induced changes in platelet function using whole blood and classical light transmission aggregometry: the results of a pilot study. Anesth Analg. 2009;108(6):1747–1754.
119. Picker SM. In-vitro assessment of platelet function. Transfus Apher Sci. 2011;44(3):305–319.
120. 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):739–746.
121. Starr NE, Matthay ZA, Fields AT, et al. Identification of injury and shock driven effects on ex-vivo platelet aggregometry: a cautionary tale of phenotyping. J Trauma Acute Care Surg. 2020;89:20–28.
122. Unruh M, Reyes J, Helmer SD, Haan JM. An evaluation of blood product utilization rates with massive transfusion protocol: before and after thromboelastography (TEG) use in trauma. Am J Surg. 2019;218(6):1175–1180.
123. Einersen PM, Moore EE, Chapman MP, et al. Rapid thrombelastography thresholds for goal-directed resuscitation of patients at risk for massive transfusion. J Trauma Acute Care Surg. 2017;82(1):114–119.
124. Stettler GR, Sumislawski JJ, Moore EE, et al. Citrated kaolin thrombelastography (TEG) thresholds for goal-directed therapy in injured patients receiving massive transfusion. J Trauma Acute Care Surg. 2018;85(4):734–740.
125. Stettler GR, Moore EE, Nunns GR, et al. Rotational thromboelastometry thresholds for patients at risk for massive transfusion. J Surg Res. 2018;228:154–159.
126. Cunningham AJ, Condron M, Schreiber MA, et al. Rotational thromboelastometry predicts transfusion and disability in pediatric trauma. J Trauma Acute Care Surg. 2020;88(1):134–140.
127. Mauffrey C, Cuellar DO 3rd, Pieracci F, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. Bone Joint J. 2014;96-B(9):1143–1154.
128. Stensballe J, Ostrowski SR, Johansson PI. Viscoelastic guidance of resuscitation. Curr Opin Anaesthesiol. 2014;27(2):212–218.
129. Walsh M, Thomas SG, Howard JC, et al. Blood component therapy in trauma guided with the utilization of the perfusionist and thromboelastography. J Extra Corpor Technol. 2011;43(3):162–167.
130. Tapia NM, Chang A, Norman M, et al. TEG-guided resuscitation is superior to standardized MTP resuscitation in massively transfused penetrating trauma patients. J Trauma Acute Care Surg. 2013;74(2):376–378.
131. Yao D, Li Y, Wang J, Yu W, Li N, Li J. Effects of recombinant activated factor VIIa on abdominal trauma patients. Blood Coagul Fibrinolysis. 2014;25(1):33–38.
132. Kashuk JL, Moore EE, Sawyer M, et al. Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. Ann Surg. 2010;251(4):604–614.
133. Holcomb JB, Minei KM, Scerbo ML, et al. Admission rapid thrombelastography can replace conventional coagulation tests in the emergency department: experience with 1974 consecutive trauma patients. Ann Surg. 2012;256(3):476–486.
134. Pezold M, Moore EE, Wohlauer M, et al. Viscoelastic clot strength predicts coagulation-related mortality within 15 minutes. Surgery. 2012;151(1):48–54.
135. Sawyer MM, Myers G, Humphrey J, Chandler M. Trauma and thrombelastography: how changes in the understanding of coagulopathy, testing, and hospital systems have changed one group's practice. Semin Cardiothorac Vasc Anesth. 2012;16(3):142–152.
136. Kashuk JL, Moore EE, Wohlauer M, et al. Initial experiences with point-of-care rapid thrombelastography for management of life-threatening postinjury coagulopathy. Transfusion. 2012;52(1):23–33.
137. Durila M, Malosek M. Rotational thromboelastometry along with thromboelastography plays a critical role in the management of traumatic bleeding. Am J Emerg Med. 2014;32(3):288.e1–288.e3.
138. 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.
139. Schochl H, Nienaber U, Maegele M, et al. Transfusion in trauma: thromboelastometry-guided coagulation factor

concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care. 2011;15(2):R83.
140. Schochl H, Maegele M, Solomon C, Gorlinger K, Voelckel W. Early and individualized goal-directed therapy for trauma-induced coagulopathy. Scand J Trauma Resusc Emerg Med. 2012;20:15.
141. Schochl H, Schlimp CJ, Voelckel W. Potential value of pharmacological protocols in trauma. Curr Opin Anaesthesiol. 2013;26(2):221–229.
142. Schochl H, Schlimp CJ, Voelckel W. Perioperative coagulation management in multiple trauma patients based on viscoelastic test results. Unfallchirurg. 2014;117(2):111–117.
143. Schlimp CJ, Voelckel W, Inaba K, Maegele M, Schochl H. 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.
144. Tanaka KA, Bolliger D, Vadlamudi R, Nimmo A. Rotational thromboelastometry (ROTEM)-based coagulation management in cardiac surgery and major trauma. J Cardiothorac Vasc Anesth. 2012;26(6):1083–1093.
145. Deng Q, Hao F, Wang Y, Guo C. Rotation thromboelastometry (ROTEM) enables improved outcomes in the pediatric trauma population. J Int Med Res. 2018;46(12):5195–5204.
146. Gorlinger K, Perez-Ferrer A, Dirkmann D, et al. The role of evidence-based algorithms for rotational thromboelastometry-guided bleeding management. Korean J Anesthesiol. 2019;72(4):297–322.
147. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. N Engl J Med. 1994;331(24):1601–1606.
148. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. N Engl J Med. 1996;335(10):701–707.
149. Ginzburg E, Cohn SM, Lopez J, Jackowski J, Brown M, Hameed SM. Randomized clinical trial of intermittent pneumatic compression and low molecular weight heparin in trauma. Br J Surg. 2003;90(11):1338–1344.
150. Allen CJ, Hsu A, Murray CR, et al. Risk of pulmonary embolism with repair or ligation of major venous injury following penetrating trauma. J Trauma Acute Care Surg. 2015;78(3):580–585.
151. Kane I, Ong A, Orozco FR, Post ZD, Austin LS, Radcliff KE. Thromboelastography predictive of death in trauma patients. Orthop Surg. 2015;7(1):26–30.
152. Cotton BA, Minei KM, Radwan ZA, et al. Admission rapid thrombelastography predicts development of pulmonary embolism in trauma patients. J Trauma Acute Care Surg. 2012;72(6):1470–1477.
153. Gary JL, Schneider PS, Galpin M, et al. Can thrombelastography predict venous thromboembolic events in patients with severe extremity trauma? J Orthop Trauma. 2016;30(6):294–298.
154. Chapman BC, Moore EE, Barnett C, et al. Hypercoagulability following blunt solid abdominal organ injury: when to initiate anticoagulation. Am J Surg. 2013;206(6):913–917.
155. Leeper CM, Vissa M, Cooper JD, Malec LM, Gaines BA. Venous thromboembolism in pediatric trauma patients: ten-year experience and long-term follow-up in a tertiary care center. Pediatr Blood Cancer. 2017;64(8):e26415.
156. 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):663–668.
157. Scharbert G, Auer A, Kozek-Langenecker S. Evaluation of the platelet mapping assay on rotational thromboelastometry ROTEM. Platelets. 2009;20(2):125–130.
158. Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by thrombelastography platelet mapping. Br J Anaesth. 2009;102(4):492–498.
159. Daley MJ, Trust MD, Peterson EJ, et al. Thromboelastography does not detect preinjury antiplatelet therapy in acute trauma patients. Am Surg. 2016;82(2):175–180.
160. Karon BS, Tolan NV, Koch CD, et al. Precision and reliability of 5 platelet function tests in healthy volunteers and donors on daily antiplatelet agent therapy. Clin Chem. 2014;60(12):1524–1531.
161. Connelly CR, Yonge JD, McCully SP, et al. Assessment of three point-of-care platelet function assays in adult trauma patients. J Surg Res. 2017;212:260–269.
162. Yeung MCF, Tong SYT, Tong PYW, Cheung BHH, Ng JYW, Leung GKK. Use of viscoelastic haemostatic assay in emergency and elective surgery. Hong Kong Med J = Xianggang yi xue za zhi. 2015;21(1):45–51.
163. Benes J, Zatloukal J, Kletecka J. Viscoelastic methods of blood clotting assessment - a multidisciplinary review. Front Med. 2015;2:62.
164. Dunham CM, Rabel C, Hileman BM, et al. TEG(R) and RapidTEG(R) are unreliable for detecting warfarin-coagulopathy: a prospective cohort study. Thromb J. 2014;12(1):4.
165. Franchi F, Hammad JS, Rollini F, et al. Role of thromboelastography and rapid thromboelastography to assess the pharmacodynamic effects of vitamin K antagonists. J Thromb Thrombolysis. 2015;40(1):118–125.
166. Dias JD, Norem K, Doorneweerd DD, Thurer RL, Popovsky MA, Omert LA. Use of thromboelastography (TEG) for detection of new oral anticoagulants. Arch Pathol Lab Med. 2015;139(5):665–673.
167. Bowry R, Fraser S, Archeval-Lao JM, et al. Thrombelastography detects the anticoagulant effect of rivaroxaban in patients with stroke. Stroke. 2014;45(3):880–883.
168. Bliden KP, Chaudhary R, Mohammed N, et al. Determination of non-vitamin K oral anticoagulant (NOAC) effects using a new-generation thrombelastography TEG 6s system. J Thromb Thrombolysis. 2017;43(4):437–445.
169. Davis PK, Musunuru H, Walsh M, Mitra R, Ploplis V, Castellino FJ. The ex vivo reversibility of dabigatran-induced whole-blood coagulopathy as monitored by thromboelastography: mechanistic implications for clinical medicine. Thrombosis and Haemostasis. 2012;108(3):586–588.
170. Myers SP, Dyer MR, Hassoune A, et al. Correlation of thromboelastography with apparent rivaroxaban concentration: has point-of-care testing improved? Anesthesiology. 2020;132(2):280–290.
171. Ali JT, Daley MJ, Vadiei N, et al. Thromboelastogram does not detect pre-injury anticoagulation in acute trauma patients. Am J Emerg Med. 2017;35(4):632–636.
172. Hewes HA, Christensen M, Taillac PP, Mann NC, Jacobsen KK, Fenton SJ. Consequences of pediatric

undertriage and overtriage in a statewide trauma system. J Trauma Acute Care Surg. 2017;83(4):662–667.
173. Pracht EE, Tepas JJ 3rd, Langland-Orban B, Simpson L, Pieper P, Flint LM. Do pediatric patients with trauma in Florida have reduced mortality rates when treated in designated trauma centers? J Pediatr Surg. 2008;43(1): 212–221.
174. Russell RT, Maizlin II, Vogel AM. Viscoelastic monitoring in pediatric trauma: a survey of pediatric trauma society members. J Surg Res. 2017;214:216–220.
175. Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. Atlanta, GA: National Center for Injury Prevention and Control; Division of Unintentional Injury Prevention; 2015.
176. Ryan ML, Van Haren RM, Thorson CM, et al. Trauma induced hypercoagulablity in pediatric patients. J Pediatr Surg. 2014;49(8):1295–1299.
177. Vogel AM, Radwan ZA, Cox CSJ, Cotton BA. Admission rapid thrombelastography delivers real-time "actionable" data in pediatric trauma. J Pediatr Surg. 2013;48(6):1371–1376.
178. Leeper CM, Neal MD, McKenna C, Billiar T, Gaines BA. Principal component analysis of coagulation assays in severely injured children. Surgery. 2018;163(4):827–831.
179. Wirtz MR, Baumann HM, Klinkspoor JH, Goslings JC, Juffermans NP. Viscoelastic testing in trauma. Semin Thromb Hemost. 2017;43(4):375–385.
180. Kashuk JL, Moore EE, Millikan JS, Moore JB. Major abdominal vascular trauma–a unified approach. J Trauma. 1982;22 (8):672–679.
181. Howard BM, Kornblith LZ, Redick BJ, et al. Exposing the bidirectional effects of alcohol on coagulation in trauma: impaired clot formation and decreased fibrinolysis in rotational thromboelastometry. J Trauma Acute Care Surg. 2018; 84(1):97–103.
182. Howard BM, Kornblith LZ, Redick BJ, et al. The effects of alcohol on coagulation in trauma patients: interpreting thrombelastography with caution. J Trauma Acute Care Surg. 2014;77(6):862–865.
183. Spoerke N, Underwood S, Differding J, et al. Effects of ethanol intoxication and gender on blood coagulation. J Trauma. 2010;68(5):1106–1111.
184. Coleman JR, Moore EE, Samuels JM, et al. Trauma resuscitation consideration: sex matters. J Am Coll Surg. 2019;228(5): 760–768.e1.
185. Mador B, Nascimento B, Hollands S, Rizoli S. Blood transfusion and coagulopathy in geriatric trauma patients. Scand J Trauma Resusc Emerg Med. 2017;25(1):33.
186. Heffernan DS, Thakkar RK, Monaghan SF, et al. Normal presenting vital signs are unreliable in geriatric blunt trauma victims. J Trauma. 2010;69(4):813–820.
187. Boldt J, Haisch G, Kumle B, Brosch C, Lehmann A, Werling C. Does coagulation differ between elderly and younger patients undergoing cardiac surgery? Intensive Care Med. 2002;28(4):466–471.
188. Blaine KP, Sakai T. Viscoelastic monitoring to guide hemostatic resuscitation in liver transplantation surgery. Semin Cardiothorac Vasc Anesth. 2018;22(2):150–163.
189. Wikkelso A, Wetterslev J, Moller AM, Afshari A. Thromboelastography (TEG) or thromboelastometry (ROTEM) to monitor haemostatic treatment versus usual care in adults or children with bleeding. Cochrane Database Syst Rev. 2016; 8:CD007871.
190. Whiting P, Al M, Westwood M, et al. Viscoelastic point-of-care testing to assist with the diagnosis, management and monitoring of haemostasis: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2015;19(58):1–228, v–vi.
191. Wang H, Robinson RD, Phillips JL, et al. Traumatic abdominal solid organ injury patients might benefit from thromboelastography-guided blood component therapy. J Clin Med Res. 2017;9(5):433–438.
192. Stettler GR, Moore EE, Moore HB, et al. Redefining postinjury fibrinolysis phenotypes using two viscoelastic assays. J Trauma Acute Care Surg. 2019;86(4):679–685.
193. Peng HT, Nascimento B, Tien H, et al. A comparative study of viscoelastic hemostatic assays and conventional coagulation tests in trauma patients receiving fibrinogen concentrate. Clin Chim Acta. 2019;495:253–262.
194. Juffermans NP, Wirtz MR, Balvers K, et al. Towards patient-specific management of trauma hemorrhage: the effect of resuscitation therapy on parameters of thromboelastometry. J Thromb Haemost. 2019;17(3):441–448.
195. Pressly MA, Parker RS, Neal MD, Sperry JL, Clermont G. Accelerating availability of clinically-relevant parameter estimates from thromboelastogram point-of-care device. J Trauma Acute Care Surg. 2020;88:654–660.

How to cite this article: Sayce AC, Neal MD, Leeper CM. Viscoelastic monitoring in trauma resuscitation. *Transfusion*. 2020;60:33–51. https://doi.org/10.1111/trf.16074