# Acute traumatic coagulopathy: The elephant in a room of blind scientists

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**ABSTRACT:** Acute traumatic coagulopathy (ATC) is the failure of coagulation homeostasis that can rapidly arise following traumatic injury, hemorrhage, and shock; it is associated with higher injury severity, coagulation abnormalities, and increased blood transfusions. Acute traumatic coagulopathy has historically been defined by a prolonged prothrombin time, although newer, more informative measurements of hemostatic function have been used to improve diagnosis and support clinical decision making. The underlying biochemical mechanisms of and best practice therapeutics for ATC remain under active investigation because of its significant correlation to poor outcomes. The wide range of hypothesized mechanisms for ATC results from the large number of symptoms, phenotypes, and altered states in these patients as observed by multiple research groups. Much like the ancient fable of blind men describing an elephant from their limited perspectives, the limited nature of clinical and laboratory tools used to diagnose coagulopathy or evaluate hemostatic function has made finding causation difficult. The prolonged prothrombin time, degree of fibrinolysis, depletion of coagulation factors and inhibitors, and general failure of the blood have all been identified as being primary indicators for ATC. Therapeutic interventions including recombinant coagulation factors, antifibrinolytics, and blood products have been used with varying degrees of success as they are used to address specific symptoms. To truly understand the causes of ATC, research efforts must recognize the complexity of the hemostatic system and get to the heart of the matter by answering the question: "Is ATC a pathological condition that develops from the observed deficiencies in coagulation, fibrinolysis, and autoregulation, or is ATC an adaptive response generated as the body attempts to restore perfusion and avoid massive organ failure?" Because patient management must proceed without definitive answers regarding the entire causative chain, the current therapeutic focus should be on using what knowledge has been gained to the patient's advantage: control hemorrhage, maintain appropriate homeostatic balances of coagulation proteins, and restore oxygen perfusion. (*J Trauma Acute Care Surg.* 2017;82: S33–S40. 

## COAGULOPATHIES OF TRAUMA

Great strides have been made in improving early mortality rates following trauma, from the development of standardized massive transfusion protocols to improved hemostasis through the use of tourniquets. Despite the many recent advances in trauma care, failure of hemostasis following hemorrhage and shock remains a leading cause of death.[1]

One of the primary elements of this hemostatic failure is the development of early coagulopathies.[2–4] Historically, the prothrombin time (PT) and its calculated international normalized ratio (INR) have been used to identify early coagulation deficiencies and guide decision making in emergency medicine and transfusion.[2,4–6]

A patient is defined as hypocoagulopathic if the INR is determined to be above a specific value; typically 1.2 to 1.5 (for patients not prescribed anticoagulants) is used as the delineator, based on the evidence showing that patients with higher values require more transfusions and suffer higher mortality.[7,8] However, there are often patients who present with a hypercoagulopathy (shortening of PT) following trauma,[9] particularly in conjunction with burn injury.[10] This hypercoagulable state may or may not transition into a hypocoagulable state as shock continues to develop.[11] Determining whether these are distinct classes of coagulopathies or merely different phases of a common syndrome is difficult because of the rapid physiological changes occurring in these patients. This article primarily focuses on the hypocoagulable states that are recognized as predicting poor clinical outcomes, frequently observed as patients arrive in emergency departments.

The syndrome of trauma-induced coagulopathy (TIC) can occur anytime following injury, particularly in response to coagulation factor dilution as a result of the infusion of resuscitation fluids, acidosis, sepsis, or hypothermia; it can continue for several days.[12] When presenting early (as soon as 30 minutes after trauma prior to intervention), the phenomenon is termed acute traumatic coagulopathy (ATC).[13–15] It remains unknown whether patients are preconditioned for ATC or whether specific injury patterns may predispose patients to particular coagulopathies.[16] The mechanisms underlying ATC remain an active area of research because of the implications this diagnosis has for outcomes.[13]

This review explores the phenomenon of ATC from the following perspectives. A brief discussion on why ATC has been difficult to understand from a mechanistic perspective is followed by an examination of the many causation hypotheses that have arisen from the study of ATC and trauma in general. Then, the methodologies and targets of interest in current research avenues of exploration are outlined. Finally, support for a holistic approach

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to future ATC studies leads into some indications of how treatment should proceed in the meantime.

## A DIFFICULT RESEARCH PROBLEM

It has been difficult to study ATC (and TIC more broadly) in humans for a number of logistical reasons. Timely sample collection is difficult because these patients are vulnerable and undergoing batteries of tests and surgical interventions. While dispensations can be granted to collect patient samples during the acute period where consent may be impossible, there are no baseline preinjury measurements against which to compare clinical data.

Even when early samples are available, there are discrepancies in the diagnostic tests. Some optically based tests are for plasma only, whereas others are intended for whole blood. One concern is that plasma does not incorporate all blood elements. Another concern is that hemostatic deficiencies in the microcirculation where hematocrit is significantly lower may be masked by using blood drawn through peripheral veins.[17]

The routine plasma-based PT/activated partial thromboplastin time (aPTT) tests were developed to monitor hemophilia and other coagulation disorders and have not been validated for acute hemorrhage during trauma. While many other tools have been developed to complement or replace these standard tests,[18] they are limited in scope and conclusiveness, providing results that indicate a phenotype and not necessarily a cause.[19–22] Coagulopathies are time-dependent processes with potentially drastic changes in the acute phase, but clinical assays provide only snapshots of information about blood drawn remotely from the site(s) of injury often many minutes prior to determining results. Thus, many laboratory tests fail to facilitate an understanding of the dynamic nature of coagulation changes. Tests that collect time of clot formation as the end point, such as clot-based factor assays, are essentially PT or aPTT mixing studies of factor-depleted and patient plasma. These assays are not validated for use in the setting of multiple factor deficiencies in combination with hemodilution and other homeostatic perturbations. The presence of high concentrations of prothrombotic microparticles, cell-free DNA, and other cellular debris could easily affect results. The lack of a precise connection and method of calibration between devices and methodologies increases susceptibility to misinterpretation, leading to the potential of conflicting research conclusions and false clinical diagnoses.

These shortcomings of clinical research have likely been the cause of the large variety of conclusions that have been drawn by those attempting to elucidate the biochemical mechanisms underlying ATC. Much like the ancient fable of the blind men attempting to identify an elephant by touching it in different places, reaching incomplete conclusions from their limited perspectives, many theories have been put forth to describe the causes of ATC that have been derived by looking at one portion of the phenotype. Table 1 summarizes these sometimes conflicting theories, which are expanded in the following section.

## PREVIOUS STUDIES (AND THEIR CONCLUSIONS)

### The Protein C Pathway—Patients Are Anticoagulated

The driving forces behind ATC have been ascribed to a number of different elements within the hemostatic environment. Many studies observed that hypoxia and ischemia led to a loss of protein C (PC) and an increase in activated protein C (aPC). These studies also observed a concomitant reduction in factor (F) V and FVIII levels, leading investigators to hypothesize that aPC was excessively cleaving activated FV and FVIII, thus diminishing thrombin generation potential.[5,23–27] The deficiency of multiple factors in the setting of PC activation suggests that the patient is anticoagulated, but this theory has been questioned by studies showing that apart from fibrinogen the factors at large are only moderately impaired after trauma.[28] Two recent in vitro studies have independently shown that a concentration of aPC orders of magnitude higher than what has been measured in ATC patients is required to negatively impact hemostasis alone.[29,30] While aPC certainly contributes to reduction of thrombin generation through negative feedback inhibition, significant amounts of thrombin would be required to produce an anticoagulant concentration of aPC. Thrombin generation in trauma patient blood appears sufficient to produce coagulation, as there is generally some degree of hypercoagulability (elevated thrombin potential) in ATC.[31–33] High thrombin-antithrombin and prothrombin fragment levels demonstrate that, indeed, large amounts of thrombin are generated in both ATC and non-ATC trauma patients,[7,8] which is difficult to reconcile with what it means to be anticoagulated. A recent study suggests that the third leg of the lethal triad of trauma, acidosis, may even heighten thrombin activity because of decreased antithrombin activity.[34]

### Fibrinogen Depletion

A depletion of fibrinogen has been implicated as a mechanism for ATC; many trauma patients present with diminished fibrinogen, which is correlated with poor survival.[35] As the terminal substrate for the coagulation cascade, fibrinogen must be maintained at a minimal level lest the hemostatic enzymatic response be in vain. A porcine model of trauma demonstrated a net loss of fibrinogen despite continued synthesis of fibrinogen throughout;[36] a similar loss was observed in a rat polytrauma ATC model.[37] The decreased levels of fibrinogen observed clinically clearly correlate to the development of coagulopathies.[38]

**TABLE 1.** Potential Pathways That Lead to the Phenotypes Observed in ATC Are Illustrated Along With a Citation That Describes the Evidence

| Table 1: Mechanistic Theories of ATC | | Ref |
|---|---|---|
| 1 | Tissue damage/ischemia/hypoxia → aPC → decreased thrombin generation → anticoagulation | Brohi et al[5] |
| 2 | Fibrinogen consumption/depletion → inadequate clot strength | Deras et al[35] |
| 3 | Activation of PC → binding to PAI-1 → increased fibrinolysis | Cohen et al[25] |
| 4 | Ischemia → release of tPA from endothelial surface → increased fibrinolysis | Chapman et al[39] |
| 5 | Hypercoagulation → fibrinolysis shutdown | Moore et al[40] |
| 6 | Excess thrombin → activation of PC + release of tPA + depleted fibrinogen → DIC + lysis | Johansson et al[8] |
| 7 | Ischemia/hypoxia/coagulopathy → resuscitation → endothelial damage + dilution → blood failure | Bjerkvig et al[42] |
| 8 | Ischemia/hypoxia + increased metabolic demand → platelet mitochondrial exhaustion | Pareti et al[45] |

### Excessive Fibrinolysis

Instead of simple depletion of fibrinogen, many have focused on excessive fibrinolysis as the culprit in ATC. This has also been associated with aPC, as aPC binding plasminogen activator inhibitor (PAI-1) has been hypothesized to result in a "derepression" of lysis,[25] leading to poor clot strength maintenance. However, PAI-1 inhibits aPC, and in vitro plasma studies with excess aPC showed no corresponding increases in lysis.[29,30] In an attempt to improve perfusion locally, the shock response following ischemia does result in the release of tissue plasminogen activator (tPA) from endothelium near damaged tissues; this could have a systemic fibrinolytic effect.[39]

### Fibrinolytic Shutdown

While excess fibrinolysis is correlated with poor outcomes, a "shutdown" of fibrinolysis is also incompatible with proper hemostatic function, possibly increasing microvascular thrombosis and causing multiorgan failure. Shutdown was attributed to a population with the highest mortality rate in one study.[40] True incidence rates for fibrinolytic shutdown are unknown, and as discussed later, shutdown may be indicative of poor platelet function rather than any specific enzymatic changes.

### Disseminated Intravascular Coagulation

The initial hypercoagulable aspect of blood following trauma in conjunction with the observed increase in fibrinogen degradation products has led some to conclude that ATC is actually disseminated intravascular coagulation (DIC) with a fibrinolytic phenotype.[8] One review noted that comparisons of the symptoms between patients defined as having ATC or DIC with a fibrinolytic phenotype indicated that there was insufficient reason to uniquely classify the two diagnoses;[41] the distinction could depend on the patient's stage within the progressive disorder at any given time. However, equating ATC to DIC with fibrinolysis is uninformative from a mechanistic standpoint; we still lack an understanding of how increased thrombin generation occurs in the setting of prolonged PT and how this may also be associated with either relative hyperfibrinolysis or hypofibrinolysis.

### Hypoxic Blood Failure

While much of the discussion around coagulopathy concerns the effects of hemorrhagic shock and ischemia on plasma proteins and enzymatic reactions, the impact on tissues cannot be ignored. The oxygen debt generated in ischemia has long been shown to have implications in traditional understandings of organ failure, but new evidence suggests that the endothelium and blood are inherently linked as an organ and are affected together depending on the degree of hypoperfusion.[42] Ongoing blood loss, hemodilution from crystalloids, hypothermia, and acidosis that occur during persistent hemorrhage and resuscitation further intensify the severity of ATC and may cause an all-encompassing "blood failure."

### Platelet Dysfunction

Maintaining vascular integrity after trauma is strongly dependent on functional platelets that activate, accumulate at the injury, provide a scaffold to initiate thrombin generation, and, through clot retraction, participate in mechanical hemostasis by defining and reconnecting damaged vascular tissue edges. Platelet dysfunction can thereby result in increased bleeding and mortality and is thought to be an early, sensitive indicator of ATC. However, the full impact that shock, hypoxia, and ischemia-reperfusion injury have on platelets is still being defined. Despite platelets' importance, early clinical recognition of platelet dysfunction is limited, as the aforementioned, plasma-only PT/aPTT tests neglect platelets completely. Even viscoelastic tests that do provide some measure of platelet function are somewhat insensitive metrics for assessing ATC.[43] Some have suggested that platelet refractoriness occurs because of "platelet exhaustion,"[44,45] whereas others have hypothesized differential platelet activation patterns based on regional or clot structural hierarchy.[46] In storage, platelets undergo bioenergetic failure leading to mitochondrial damage, induction of apoptosis, and loss of function.[47] Hypoxic conditions are known to induce free radical production and cause oxidative stress, increased intracellular calcium, and cell death. A bioenergetic failure within the body's platelets may also be a component of ATC.

## ANSWERING UNANSWERED QUESTIONS

Returning to the analogy of the blind men examining the elephant, the different tools, assays, and phenotypic observations used in ATC patients have led to the variety of (sometimes) conflicting theories on the origins of ATC; these in turn have led to a number of conclusions regarding how ATC patients should best be treated. There remain questions and problems associated with each tool, proposed mechanism, and potential treatment (Fig. 1), and the remainder of this review focuses on current undertakings to elucidate ATC.

### Coagulation Factors

Clinical measurements of coagulation factors are frequently collected using assays whose primary reagents are plasmas deficient in the factor of interest. This plasma is forced to clot through intentional overactivation of the coagulation cascade—essentially a modified PT or aPTT. The test results actually illustrate the maximal ability of the patient's plasma to support the conversion of prothrombin to thrombin and fibrinogen to fibrin; these metrics are compared against normal standards to generate an activity level for a single factor. Unfortunately, these tests may not be appropriate in a patient who is presenting with consumptive and/or dilutional coagulopathy, because each factor's assay assumes that all other factors are within reference ranges and can participate in clot formation. In addition, a significant fraction of many factors will be unavailable for the activity assay as they adhere to cell surfaces and participate in coagulation. This makes factor-specific assay testing inconclusive in the context of ATC where many or all other factors are changing, especially when the assays' end points are clot times.

Some assays use fluorogenic or chromogenic responses to examine rates of enzyme formation, but they suffer from a common flaw: these tests are designed to convert every available zymogen into its active form, and thus they describe the total enzyme availability rather than the actual active form that is participating in clot formation in vivo. In addition, it is difficult to measure active enzymes in blood samples because of the presence of inhibitors or other changing environmental conditions. Thus, another battery of tests invokes the use of tissue factor

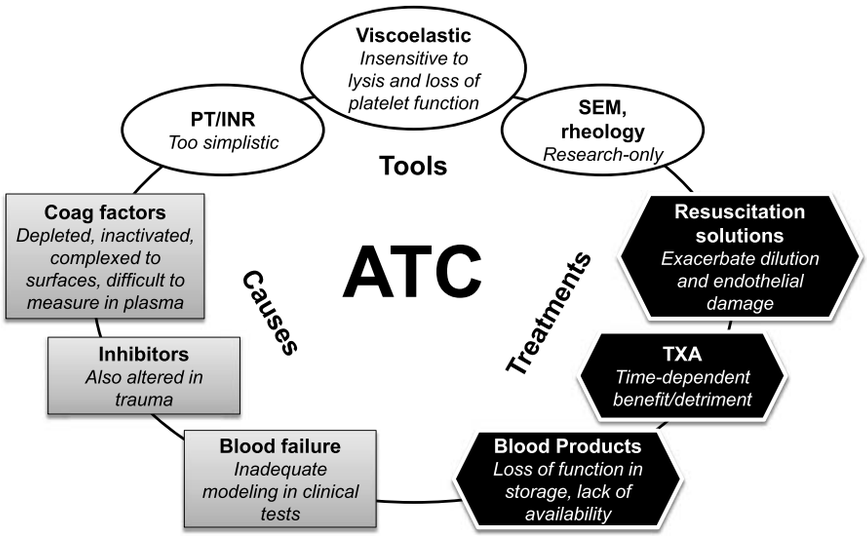


**Figure 1.** Highlighting the difficulty of understanding and treating patients with ATC and TIC, shown are examples of the tools used for diagnosis, the biochemical mechanisms hypothesized as root causes of the phenomena, and the treatments available to restore perfusion and hemostasis in the bleeding patient. Each element has an associated problem or difficulty.

or contact pathway activators to initiate a massive enzymatic conversion (e.g., the calibrated automated thrombogram[48]). These tests therefore give information about the *potential* of an individual to produce active enzyme, rather than the *current* level of active enzyme, and they give little information about which enzyme(s) is deficient should a decreased value be observed.

When fluorogenic substrates were used to measure the levels of active thrombin and plasmin in both rat and human normal plasma samples, they were found to be very low.[49] By introducing FXa to convert all prothrombin to thrombin or adding tPA to convert all plasminogen to plasmin, the total available amounts of prothrombin and plasminogen were determined to be some 30 to 100 times higher than their active forms; PC was also shown to be approximately 40 times higher than its active form. Thus, a large supply of zymogen is available in normal conditions. Deficiencies are useful for identifying consumptive coagulopathy, but in the acute phase, the results can be misleading.

Uncertainties about a patient's coagulation factors can be magnified in light of critical interactions between enzymes that are not doctrinally considered to be connected in the coagulation cascade. For instance, plasmin, known for its proteolytic activity on fibrin, can exert its effects on FV,[50] FVIII,[51] and FXIIIa,[52] among others.[53] Our laboratory has observed that increasing the amount of thrombin to levels observed in trauma and beyond will improve the rate of clot initiation but result in poorly formed clots. The kinetics of clot formation matter for hemostasis;[54] the redundancies and feedback mechanisms require a multifactorial analysis to further research efforts, not easily obtainable via standard clinical assays.

## Inhibitors

Active enzymes are also difficult to measure because of the presence of significantly higher concentrations of enzymatic inhibitors than the zymogens (and enzymes) themselves.[55] Thrombin and plasmin are rapidly removed from active circulation by inhibitors such as antithrombin, thrombomodulin, α2-antiplasmin, and α2-macroglobulin.[56,57] These inhibitors' impacts on the hemostatic system must be carefully considered within the contexts of how coagulation factors are measured, a task that becomes particularly complex as levels of inhibitors also dynamically change following trauma.[49,58]

Aside from pure inhibition, there are opposing forces at work—the balance of thrombin and plasmin is the most obvious example as these two proteases function primarily to build and destroy the fibrin network. The robust balance that exists in hemostasis must be significantly perturbed to result in a coagulopathy, suggesting that the accumulation of a number of moderate to severe alterations may be more potent than a large imbalance at one point within the clotting cascade.

## Endothelial Elements

The complexity of the endothelial surface is one of many additional elements outside the scope of clinical measurements. However, endothelial activation in response to trauma, inflammation, and ischemia can be detected in blood or plasma through the release of a variety of hemostatically relevant proteins (both procoagulant and anticoagulant), signaling molecules, and endothelial glycocalyx components.[59] This includes an increase in the number of circulating microparticles generated from a number of cell types, which provokes a higher level of variance in the coagulation response.[60–62] While the effects of these shed elements can be observed ex vivo, the ongoing participation of the endothelial and subendothelial surfaces is generally missed in coagulation assays.

## Viscoelastic Testing

The simplicity of the PT/aPTT tests makes them clinically attractive, even though the conclusions that can be drawn from a single data point are suspect. There is no correlation between a clinically observable bleeding diathesis (e.g., validated pathological bleeding scale score) in trauma patients and PT/aPTT results; these plasma-based assays are inappropriate for hemorrhage

assessment. In the past 25 years, more than 20 studies (including nearly 5,000 surgical or trauma patients) have shown that viscoelastic hemostatic assays provide an earlier detection of coagulopathy and may be more accurate indicators of transfusion requirements than PT/aPTT.[63] While PT and aPTT give only a clot time, the viscoelastic assays can account (to a degree) for the influence of cellular elements in hemostasis (including platelet function) and provide additional end points including clot formation, stability, and strength. Viscoelastic testing of whole blood may also identify changes in clot strength and breakdown, which in turn could provide insights into deficiencies and/or dilutions of clotting factors and cellular components in resuscitation-independent and -dependent coagulopathies, respectively. Thus, these assays have filled a major diagnostic void in transfusion management, although more standardization and validation are needed for widespread adoption.[64]

However, even when viscoelastic testing is used, it is easy to draw conclusions that may describe the phenotype but miss the actual cause. An example of this is the discrepancy between hyperfibrinolysis and fibrinolytic shutdown. When a platelet-containing sample is subjected to viscoelastic testing, a certain degree of lysis is expected—between 0% and 8%.[65,66] Hyperfibrinolysis is not typically diagnosed until 15% of the maximal clot strength is lost,[67] although there is disagreement on what constitutes clinically relevant lysis in bleeding patients, with some arguing that lysis greater than 3% is significant.[68] However, plasma-only samples with a full complement of coagulation and fibrinolytic factors have very low expected degrees of lysis.[29] This discrepancy illustrates the underappreciated contribution of platelets to the biophysical phenomena taking place within the testing chamber. In the presence of functional platelets, the retraction of the clot that occurs as the platelets' cytoskeletal rearrangement promotes clot firmness can result in a decreased amplitude measurement and be identified as lysis of the clot.[69] When no platelets are present, this "lysis" effect is not observed. Therefore, it is possible that in some patients fibrinolytic shutdown (as defined via viscoelastometry) is associated with increased mortality because those patients have dysfunctional or depleted platelets, which do not participate in clot retraction; poor platelet function and counts are known to be correlated to poor survivability.[70–72]

## Point-of-Care Hemostasis Assays

Point-of-care (POC) hemostatic assays are more attractive than conventional clinical laboratory assays as they reduce turnaround times, thus replacing empirical judgment for transfusion decisions with real-time information on hematologic abnormalities. Decisions based on empirical data alone increase transfusion rates, which are associated with increased morbidity, mortality, and economic burden.[73,74] Rapidity is critical, as many trauma fatalities are preventable with early intervention.[75] In the past decade, a number of POC assays have emerged at several stages along the "bench-to-bedside" transition.[76] Miniaturized devices assess coagulation under pathophysiologic flows or under controlled conditions ex vivo, in real time, using small volumes.[77,78] POC machines can provide INR within 3 minutes. Newer variants of small, portable platelet analyzers can assess function in 2 minutes from whole blood, and other devices provide platelet counts and hematologic differentials within 5 minutes from small sample volumes.[79,80] However, several improvements are highly desirable to fully translate POC devices to the trauma setting: easy handling and processing of samples; portability, operability, and robustness of the instrument; high throughput to handle multiple treatments; and reliable, rapid, and integrated analysis. Simultaneously, further research is required to standardize and validate the utility, feasibility, and cost-effectiveness of near-patient monitoring vis-à-vis conventional laboratory assays on the clinical outcomes.

## "Research-Only" Assays

As discussed, current hemostasis assays are almost exclusively based on putting blood in a test chamber and inducing coagulation, ignoring important factors, such as endothelial interaction, shear forces, oxygen tension, and blood pressure, all of which contribute to the complexity of coagulopathy in vivo. While no in vitro system can completely account for all of these factors, the use of multiple assays under different modalities can help alleviate some of the potential discrepancies between test results and reality.[81] For instance, the use of a turbidimetric assay of fibrin polymerization can help define coagulation parameters more specifically, identifying changes to clot shape and mechanical strength, which may have been misidentified as clot lysis in viscoelastometry. Other techniques, such as rheology, electron microscopy, and use of microfluidics systems, greatly increase the fidelity of data collected on clots and clot formation and can illustrate properties and deficiencies that would otherwise be missed (or misdiagnosed) in standard tests, but translating these to the trauma ward would require ease-of-use modifications and miniaturization of the technologies or correlation with other assays.

# COMPLEXITY OF THE SYSTEM: LOOKING AT THE BIG PICTURE

While recognizing the complexity of the system at large, many clinical efforts and research studies still rely on the PT as the primary identifier to glean early diagnostic information about how to proceed along the myriad available treatment options such as blood product transfusion, usage of prothrombin complex concentrates and/or fibrinogen, volumetric resuscitation, cardiopulmonary bypass, ventilation, deployment of profibrinolytics or antifibrinolytics, and all of the decisions that must be considered in an effort to simultaneously restore perfusion to damaged tissues, minimize infection, and control hemorrhage. More illuminating information that accounts for the myriad changes and potentially underlying causes is required to optimally reduce the rates of mortality in trauma.

With all the tests that have been devised to triage, diagnose, and guide treatment of ATC, the question remains: Is ATC actually a desperate attempt to maintain perfusion in the face of ischemia, or is it the result of a maximal effort to stop bleeding, leading to failure of the blood through consumption, dilution, and/or loss of autoregulation? For instance, the fibrinolytic response could reflect physiologic efforts to restore perfusion and avoid multiorgan failure in ischemic conditions. It is difficult to distinguish whether ATC consists of the consequences of the transition from compensatory to noncompensatory regulation, or if it represents a direct attack from severe trauma due to

each of the pathological elements described. Current diagnostic criteria for ATC are thus insufficient to represent the complexity of pathophysiologic transition and progress after trauma and hemorrhagic shock. Therefore, an integrative approach to understanding the trauma patient's physiology becomes necessary to advance clinical diagnoses and treatments in ATC.

The first part of this all-encompassing approach requires a continuation of the investigation of changes at the protein level, as we understand that several relevant proteins are frequently lost from detection in ATC. This may be due to direct hemorrhage, dilution, activation and affixation to complexes, shedding, endocytosis, or cleavage and inactivation. Advancing the field from this front could mean that, instead of observing how much or little activity remains for a specific factor, an examination of all of the inactivation peptides of coagulation factors will better demonstrate the nature of being "anticoagulated" as a contributor or cause of ATC. Furthermore, seeking to view proteomic changes based on normalization with total blood protein levels could avoid incorrect inferences in the presence of dilutional effects.

A unified approach to understanding the mechanisms of ATC will benefit physiological models. The contribution of shock and ischemia may be elucidated by examining different clinical scenarios and developing new animal models. For example, a recent study demonstrated activation of hyperfibrinolysis in drowning victims,[82] lending support to the idea that hypoxemia may trigger coagulation changes that are currently seen as pathological (e.g., consumption) but in reality are adaptive. It may be fruitless or even harmful to counter hyperfibrinolysis without adequately reperfusing hypoxic organs, which is highly relevant in an era of resuscitation based on the supposed merits of permissive hypotension.

The goal is to avoid continuing down the path of the blind scientists examining the problem from multiple perspectives; the mechanistic, diagnostic, and therapeutic conclusions derived from the study of ATC should be drawn from a holistic evaluation of the syndrome.

## HOW DO WE TREAT?

The end goal of understanding the mechanisms of ATC is to better define treatment protocols and to reduce mortality and morbidity. Regardless of the inadequacies of the current understanding of ATC's causes, patients must be treated with the best possible care. Additional fibrinogen as the primary substrate for clot formation has been shown to be beneficial in a number of studies, but it may fuel the fibrinolytic chaos of DIC. While prothrombin complex concentrates and thrombogenic agents may reduce PT, they can also improperly accelerate the coagulation process in some patients, resulting in weakly formed clots and embolic phenomena. The controversy surrounding the usage of tranexamic acid, an antifibrinolytic that is effective early after injury and appears to have nearly opposite effects if given too late,[83] serves to highlight once again the need for careful study of interactions and redundancies of the hemostatic system; in fact, a recent study in an ex vivo dilutional model highlighted the importance of restoring balance through the use of multiple coagulation factors and inhibitors.[84]

The most common procedure in initial trauma management is fluid replacement, often necessary to maintain perfusion and prevent ischemic organ failure despite the number of problems affecting both short- and long-term recovery following nonhemostatic resuscitation. The use of blood products largely buffers these negative ramifications; however, transfusion strategies have yet to be perfected.[85] Types of blood products, volumes required, frequency of transfusion, and storage conditions are all under discussion.[86] It has been argued that, although the modern blood product transfusion strategies that have been used under the banner of hemostatic resuscitation provide greater benefits than crystalloid substitutes, they are still deficient at actually providing the trauma patient with improved coagulation, oxygen perfusion, and repayment of the oxygen debt.[87,88] This is due to multiple influences, not the least of which is that, even if transfused according to the damage control resuscitation protocols, blood products do not maintain their quality over the storage duration.[89,90] For this (and other logistical reasons), there has been in recent times a return to examining the transfusion of whole blood,[91] a historically significant practice[92] that has been reimplemented under strict guidelines in some portions of the United States and allied armed services.[93] Although not without risks, replacing what has been lost makes sense in the context of trauma and hemorrhage.

## CONCLUSIONS

Understanding the mechanisms that underlie ATC is important to reducing trauma mortality rates, and great strides continue to be made by the clinicians and scientists devoted to this effort. The multivariate nature of these coagulopathies requires addressing them from their root causes rather than attempting to correct symptoms or results from inconclusive laboratory tests. Clearly, the diversity of research outcomes in this field illustrates the need to consider all of the interlocking parts of coagulation as we treat, promoting strong hemostasis while simultaneously preventing massive organ failure.

While the understanding of ATC continues to improve and better tests are developed, it is, in the meantime, prudent to seek restoration of both tissue perfusion and coagulation homeostasis as the foundation of damage control resuscitation.

### DISCLOSURE

The authors declare no conflicts of interest.

### AUTHORSHIP

M.A.M. and A.P.C. conducted the literature search and wrote the manuscript. M.C.H., J.A.B., X.W., A.K.R., D.N.D., and K.M.R. conducted the literature search, contributed to the writing of the manuscript, and gave critical reviews.

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