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Is Coagulopathy an Appropriate Therapeutic Target During Critical Illness such as Trauma or Sepsis?

Hunter B. Moore[1], **Robert D. Winfield**[2], **Mayuki Aibiki**[3], and **Matthew D. Neal**[4]

[1]University of Colorado, Aurora

[2]University of Kansas Medical Center

[3]Ehime University Graduate School of Medicine

[4]University of Pittsburgh School of Medicine

Abstract

Coagulopathy is a common and vexing clinical problem in critically ill patients. Recently, major advances focused on the treatment of coagulopathy in trauma and sepsis have emerged. However, the targeting of coagulopathy with blood product transfusion and drugs directed at attenuating the physiologic response to these conditions have major potential risk to the patient. Therefore, the identification of coagulopathy as a clinical target is an area of uncertainty and controversy. In order to analyze the state of the science regarding coagulopathy in critical illness, a symposium addressing the problem was organized at the 39th annual meeting of the Shock Society in the summer of 2016. This manuscript synthesizes the viewpoints of the four expert panelists at the debate and presents an overview of the potential positive and negative consequences of targeting coagulopathy in trauma and sepsis.

Keywords

Coagulopathy; trauma; sepsis; acute coagulopathy of trauma; critical care; disseminated intravascular coagulation

Introduction

At the 39th annual meeting of the Shock Society in June of 2016, a Pro-Con debate focused on the question of whether coagulopathy is an appropriate therapeutic target during critical illness with specific focus on trauma and sepsis. Two of us (MN and MA) took the viewpoint in favor of defining coagulopathy as a therapeutic target while the others (HM and RW) highlighted risks and flaws with this approach. In the present work, we highlight the major arguments for both sides while presenting an overview of the clinical problem, recent relevant literature, and related research into the mechanisms of the disease.

Name and address for correspondence and reprint requests: Matthew D. Neal, MD; Assistant Professor of Surgery and Critical Care Medicine, Division of Trauma and Acute Care Surgery, Department of Surgery, F1271.2 PUH 200 Lothrop Street, Pittsburgh, PA 15213. (412) 647-0635 nealm2@upmc.edu.

All authors contributed equally to this work.

PRO: Coagulopathy should be a therapeutic target in critical illness

Perhaps one of the most common but least well understood clinical problems in critical illness is the presence of coagulopathy. An initial concern is the exceptionally broad definition of coagulopathy, and a discussion about ‘targeting’ coagulopathy in critical illness requires specific and detailed definitions. As Hunt outlines in her seminal review of coagulopathy in critical care, the definition of coagulopathy can include both impaired ability to form clot as well as pro-thrombotic states, and sufficient overlap exists to allow both ends of the spectrum to be present in the same individual at any given time(1). In fact, the terminology is even broader in application, as it may involve both inherited and acquired disorders of coagulation, sequelae of iatrogenic resuscitation(2), pharmacological induced states, and the entire spectrum of coagulation including platelet and endothelial effects. As such, specific definitions of coagulation disturbance are key. Ideally, specific scoring systems should be utilized to identify and define ‘coagulopathic’ patients in specific disease states, such as those devised for the acute coagulopathy of trauma(3) and DIC in sepsis(4-6). Complicating this approach, however, is the observation that significant overlap may exist between the pathobiology of certain diseases, especially in the case of diseases of microvascular injury(7).

Given the complexity of the clinical problem, it is tempting to avoid the target, which likely explains the relative dearth of investigation into coagulopathy in critical illness until recently. However, the striking observation of a number of recent clinical studies, particularly in trauma and sepsis, suggest that, in fact, targeting disease specific derangements in coagulation may well be an integral part of the management of critically ill patients. Specifically, the explosion of observational, and recently, prospective data supporting hemostatic resuscitation of trauma patients (8-10) as well as the reduction in mortality seen with early use of anti-fibrinolytic therapy (11) suggest that underlying coagulopathy corrected by these treatments may represent a previously underappreciated driver of morbidity and mortality after severe trauma. Similar enthusiasm arises for targeting coagulopathy in sepsis based on preclinical and early clinical data highlighting the role of anticoagulation in appropriately chosen patients (12-14). Specific details of these two conditions will be outlined in further detail here as an example of the promise of developing treatments for coagulopathy in critical illness.

Trauma coagulopathy

Coagulopathy in the setting of trauma is a multifactorial condition, combining iatrogenic resuscitation (2, 15) effects, prehospital medications (2, 16), and a unique endogenous coagulopathy associated with tissue injury and shock (3, 17-19). For the purposes of this discussion, the acute coagulopathy of trauma, or acute traumatic coagulopathy (ATC) refers to the latter, in which the cellular response to sterile injury results in changes in coagulation, ranging from impaired clot generation to pro-thrombotic tendencies. A thorough review of all the proposed mechanisms of ATC is outside the scope of this work, but we seek here to highlight the definitions, treatment strategies, and recent advances in the basic science investigations of therapeutic targets.

Definition (INR vs TEG vs Clinical coagulopathy)—The acute coagulopathy of trauma is present in as many as 30% of critically ill patients upon arrival to the emergency department and has been shown to be an independent predictor of mortality (20). However, a challenge in the field is choosing a defining laboratory or clinical assessment tool and the early identification of patients presenting with or at risk for coagulopathy. Conventional coagulation testing was initially used to define ATC, with the INR chosen as a screening tool in many studies (20-23). However, over the past 5 years, it has become well accepted in the trauma community that the INR is an inferior test to viscoelastic testing such as thromboelastography (TEG) (24-26). Although a systematic review found insufficient data to support this conclusion (27), the review is inherently flawed. Each of the included studies in the review utilized conventional coagulation testing (prothrombin time and INR) as the 'gold standard' to which viscoelastic tests were compared. None of these conventional coagulation assays were designed for, or validated in, trauma patients and as such cannot be concluded to be a gold standard that accurately defines coagulopathy. In addition, the systematic review was published prior to the first Level 1 evidence to emerge in support of the use of TEG (26). Recently, two of us (HBM and MDN) have focused on identifying and quantifying the clinical manifestations of ATC with the goal of creating a common nomenclature as well as a clinical score for more accurate comparisons and communications in coagulopathy research (3).

Importance of targeting coagulopathy in trauma—The major advances in trauma care over the past decade have been in the design of resuscitation strategies to target coagulopathy. Beginning with the landmark study by Borgman and colleagues published from the military experience in Iraq(8), a surge of observational literature in support of ratio based resuscitation of massive hemorrhage has culminated in two key prospective analyses in support of high ratio administration of blood components to the massively bleeding trauma patient (9, 10). The PROMMPT trial was the first observational trial to provide data to assess the role of fixed ratio transfusion in response to massive hemorrhage in trauma. Perhaps the most important observation from PROMMPT was that time was of the essence; the mortality benefit seen with high ratio component therapy was realized within the first six hours, where 81% of deaths from hemorrhage occurred (9). These findings were followed by the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) multicenter trial(10) which analyzed the outcomes of patients randomized to 1:1:1 or 1:1:2 component therapy. Although no difference was observed in the primary outcomes of 24 hour or 30 day mortality, the authors did observe a significant decrease in deaths due to exsanguination and earlier hemostasis in the highest ratio group(10). Taken together, these prospective observations lend tremendous strength to the hypothesis that early resuscitation of, or potentially prevention of, trauma induced coagulopathy improves outcomes. Finally, specific pharmacotherapy targeted at inhibiting fibrinolysis after severe injury has been shown to reduce mortality in both civilian and military medicine. In perhaps the largest randomized trial ever conducted in injured patients at risk for bleeding, the CRASH II trial showed an all-cause reduction in mortality of 1.6% in patients receiving the anti-fibrinolytic drug, tranexamic acid(11). Importantly, overall transfusion requirements were no different in patients receiving tranexamic acid, and the study was limited by a lack of measurements of effect on coagulopathy to suggest that inhibition of fibrinolysis specifically leads to the

documented benefit. A more pronounced benefit was observed in the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study (MATTERS), which, within the limitations of a retrospective analysis, showed a nearly 14% reduction in mortality in patients requiring massive transfusion in patients who received tranexamic acid along with a reduction in coagulopathy despite the fact that patients in the group receiving tranexamic acid were more severely injury than those who did not receive the drug(28). In summary, a preponderance of observational data as well as Level 1 evidence in the form of the PROPPR and CRASH II trials support that resuscitation strategies where the primary intervention represents targeting the treatment and/or prevention of coagulopathy improve mortality in trauma.

Mechanisms and potential targets of trauma-induced coagulopathy—Given these advances, a thorough understanding of the mechanisms leading to the development of impaired hemostasis and coagulation disturbance is key. An important early recognition is the broad spectrum of disarray in coagulation that occurs following trauma, and thus it is highly unlikely that one molecular target or subsequent therapy is appropriate for all patients with ‘coagulopathy.’ Three key areas of basic science investigation were reviewed as potential contributors to ATC at the Shock Society symposium: the activated Protein C (aPC) pathways, early platelet dysfunction following trauma, and the spectrum of fibrinolysis, ranging from hyperfibrinolysis leading to bleeding to fibrinolysis ‘shut-down’ as coined by the Denver research group(17) and an associated thrombotic risk. The contributions of aPC and platelet dysfunction are reviewed below, and a discussion of the effects of fibrinolysis appears in the ‘con’ section of this manuscript.

Activated Protein C (aPC)—Strong evidence exists to suggest that at least one form of ATC is mediated by activation of the protein C system. Protein C is a serine protease which, upon activation, is responsible for proteolytic cleavage of factors Va and VIIa and additionally inhibits plasminogen activator inhibitor 1 (PAI-1). Tissue injury combined with shock has been shown to result in a rapid activation of protein C with a resulting state of hypocoagulability that has been estimated to be present in up to 25-40% of trauma patients (29), and trauma patients have been found to have an increase in aPC (9). In murine models, the use of antibody inhibitory strategies to block aPC attenuates coagulopathy following trauma (30). The robust and excessive activation of protein C after severe injury and shock is hypothesized to lead to protein C depletion and a subsequent transition to a hypercoagulable state, which may be linked to subsequent organ injury and mortality (19, 31). Some have challenged the role of aPC in trauma, including ex vivo studies suggesting that the levels of aPC in trauma are insufficient to exert an effect on coagulation (32), and work by Chapman and colleagues showed that excessive tPA release and not aPC mediated PAI-1 inhibition leads to hyperfibrinolysis in severely injured patients (33). Interestingly, aPC plays an additional role in maintaining endothelial barrier integrity, and so the loss of aPC following an initial surge after trauma may help to explain why conditions associated with impaired permeability and common to trauma, such as acute lung injury and infection, could be linked to aPC dysregulation (34-36).

Platelet dysfunction—It has been suggested that platelet dysfunction is one of the earliest indicators of ATC (37, 38). Given their critical roles in hemostasis and inflammation, platelets are a logical cellular target for investigation as a link between the excessive inflammatory response after injury and the regulation of thrombosis. The degree of platelet dysfunction following trauma is profound, with some reports suggesting that up to 45% of patients on admission and 90% of patients in the intensive care unit after trauma have impaired response to platelet agonists (39), with even minimally injured patients manifesting with some dysfunction(40). Importantly, impaired response to platelet agonists has been linked to mortality following trauma(41). Trauma has been shown to result in a release of endogenous danger signals, known as damage associated molecular pattern (DAMP) molecules, which are activators of the innate immune system (42). DAMP signaling through critical innate immune receptors like the Toll like receptors (TLRs) has recently been implicated in the pathophysiology of coagulopathy after trauma (43, 44) and the common thrombotic complications after trauma, such as deep vein thrombosis (45). Ding and colleagues discovered that expression of TLR4 on platelets was necessary and sufficient to regulate sequestration of platelets in the lung following hemorrhagic shock, although the ligand for platelet TLR4 was unknown (43). Subsequent studies from the same group revealed that expression release of the endogenous danger signal and TLR4 ligand, high mobility group box 1 (HMGB1), from platelets following trauma in both humans and mice resulted in autocrine and paracrine platelet activation, leading to a phenotype of microvascular thrombosis and lung and liver injury in a murine model of polytrauma and hemorrhage (44). These critical mechanistic insights, whereby sterile injury and shock result in systemic activation of platelets with sequestration and microvascular thrombosis in end organs provided critical insight to the phenomenon of ‘platelet exhaustion,’ which had long been hypothesized as a mechanism by which excessive activation of platelets following injury contributed to a spectrum ranging from impaired hemostasis to organ damage (37, 46).

Coagulopathy in sepsis

Differentiation of Type of Disseminated Intravascular Coagulation (DIC)—DIC developing as a complication of sepsis is characterized by an elevation of plasmin activator inhibitor-1 (PAI-1) leading to alterations in fibrinolysis and microvascular thrombotic complications (47). Although microvascular injury in trauma and hemorrhagic shock may bear some similarities to DIC, the impairment in hemostasis seen from hyperfibrinolysis in trauma is contrasted from sepsis (37) which seldom has a bleeding tendency but is more frequently characterized by thrombotic sequelae. So, it is requisite to address these differences in the time course changes as well as the phenotypes of DIC. Thus, considerable interest has emerged surrounding the administration of anti-coagulants such as anti-thrombin (AT) agent or human recombinant thrombomudulin (rh-TM) (37) as specific examples of targeting coagulopathy in sepsis.

Sepsis with Coagulopathy—Interventions for causes of infection are crucial for the treatment of sepsis, which should be done in parallel with respiratory, hemodynamic, and nutritional management(48). This has been performed globally as “bundle therapy” for severe sepsis. Although the survival rate for severe sepsis has improved over a decade after

the implementation of bundle therapy(49), sepsis remains a leading cause of mortality in critically ill patients. It is well known that the presence of coagulopathy leads to worse outcomes in sepsis(50). Therefore, additional therapeutic interventions to target coagulopathy such as anti-coagulation treatments for severe sepsis complicated with DIC are of particular interest. Such treatments have been performed in Japan using AT agent or rh-TM, but have not been done in the Western countries. Interestingly, AT therapy has not been included as part of the Surviving Sepsis Campaigning Guidelines(48) despite subgroup analyses in which AT agent clearly produced significant improvements in survival in septic patients with DIC(12, 13).

The treatment effects of anti-coagulation agents (AT and/or rh-TM) for patients diagnosed using the criteria of acute DIC developed by the Japanese Association of Acute Medicine (JAAM DIC criteria)(51) have recently been evaluated as part of a Japanese national-wide prospective registry study named J-SEPTIC DIC Study. JAAM DIC criteria demonstrate high sensitivity and specificity for the diagnosis of DIC(52), and all patients diagnosed with the JAAM criteria were further examined by the criteria of the International Society of Hemostasis and Thrombosis (ISTH) as overt DICs(53). The registry of the JSEPTIC DIC(54) study enrolled 3195 cases with severe sepsis/septic shock over a two-year interval between 2011-2013, with a critically ill population as demonstrated by high mean APACHE II scores (23.1 ± 8.7) and an overall in-hospital mortality rate of 34%. Patients identified as having DIC who were administered anti-coagulation therapy received anti-thrombin first as standard of care, and rh-TM was added if AT was deemed to be ineffective in treating DIC. In septic DIC patients receiving the anti-coagulation therapy grading at APACHE II scores 20-30, the adjusted odds ratio of the hospital mortality was much lower as compared to that in patients without the therapy (0.67: 0.49-0.92, 95% CI). This odds ratio was adjusted with gender, age, body weight, basal diseases, pre-existed coagulation abnormality, infection sites, treatments for infection sites, mechanical ventilation, hemodialysis, vasopressor usage, and γ-globulin administration. These differences existed even after determination by the DIC criteria of ISTH (Table 1). Thus, these results provide a rationale for anti-coagulation therapy for at least a subset of septic patients with DIC. Therefore, future randomized control studies are needed to investigate whether, in patients with septic DIC, the mortality rate decreases when the anti-coagulation treatments are utilized.

CON

The decision to treat coagulopathy is predicated on a clear definition of that term. As referenced above, Hunt defines coagulopathy as “a condition in which the blood's ability to clot is impaired”, but acknowledges that some “would consider that mildly abnormal results on coagulation screening without bleeding can also indicate a coagulopathy” (55). This distinction may seem semantic to some; however, there is much more at stake than establishment of meaning. While the provision of medications and component blood products to correct impaired clotting mechanisms is of unquestionable value in the patient with active hemorrhage, providing these therapies to correct laboratory abnormalities is both wasteful and places patients at risk for harm. These concepts serve as the foundation for the present discussion.

Trauma Induced Coagulopathy is a Marker of Shock and Tissue Injury, Not Pathology

The coagulopathic response to trauma is related to both a combination of severe tissue injury and hemorrhagic shock(56) and provides a nice biomarker to identify patients at high risk of mortality. This brings into question; is this hypocoaguable state pathologic, or physiologic? Over a half century ago, the beneficial effects of hypocoagulability(57) and fibrinolysis(58) were appreciated in animals subjected to near lethal hemorrhagic shock, supporting that trauma coagulopathy is a survival mechanism. However, in the actively bleeding patient it is difficult to ignore a coagulopathy that may be contributing to additional blood loss. Therefore, the balance of giving blood products to correct non-mechanically controllable bleeding must be countered with the risk of over correcting coagulopathy.

There may also be under appreciated benefits of delivering certain blood products that extend well beyond correcting a coagulopathy. While the Borgman study(8) identified increased units of plasma were associated with improved outcomes, it is argued that the survival benefit was, in reality, related to early plasma transfusions. The PROMMPT(59) and PROPPR(10) trials both supported the theory of the life-saving effects plasma related to early utilization. Neither of these studies demonstrated an exclusive survival advantage of providing plasma to patients with elevated INR or prolonged clotting times on the viscoelastic assays. This raises the question, what are the true beneficial effects from early plasma resuscitation? Plasma has been demonstrated to provide protection to the endothelium(60) and to reduce intestinal(61) and pulmonary(62) microvascular damage. Plasma also enhances metabolic recovery(63) and buffers fibrinolysis(64). In a sense, plasma is the ultimate early colloid resuscitation, and the benefit may not necessarily be related to increasing coagulation factors. The key with utilizing blood products for resuscitation is knowing when to stop. The randomized controlled trial using thromboelastogram (TEG) directed resuscitation from Denver demonstrated that less blood products were associated with improved survival(26).

This argument is also pertinent to the use of tranexamic acid (TXA) and PCC. Despite promising results from the CRASH and MATTERS study TXA use was found to increase mortality in a study from Miami(65) and provide no survival advantage for goal directed use in trauma patients with TEG detected hyperfibrinolysis(66). The evidence of a beneficial effect of a moderate level of fibrinolysis continues to grow(67) and medical blockade of a biologic system designed to keep the microcirculation patent seems counterintuitive. Speculation to the protective effects of TXA have been attributed to its anti-inflammatory effect, which has been demonstrated to reduce lung injury in rodents(68). However, correctly identifying the patients who benefit from this medication remains a challenge, and hyperfibrinolysis does not appear to be the optimal target. This goes along the same lines of using prothrombin complex concentrates (PCC) in trauma. PCC lack hundreds of unmeasured proteins compared to plasma(69) that may play a protective role in the endothelium and organ microvasculature as described in the previous paragraph. While using this medication for medically induced coagulopathy in trauma patients on blood thinners and head injuries has promising results(70), the ubiquitous use of this blood product on all trauma patients remains questionable, and prospective studies are needed. These

important prospective studies will help shed light on the etiology of the observed improvements in survival associated with early plasma resuscitation after trauma.

Treating Coagulopathy Wastes Valuable Resources

According to the most recent United States Department of Health and Human Services National Blood Collection and Utilization Survey Report, there were 76.2 units of blood collected per 1,000 adults, reflecting the lowest rates of donations in 20 years (71). These collections lead to a 5.2% overall surplus of blood products, but 10.3% of U.S. Hospitals reported at least one day in the survey year in which they were unable to meet nonsurgical blood needs, with an average of 3.3 and 1.2 days of plasma and platelet unavailability, respectively among surveyed hospitals (71). Thus, these products are justifiably considered a scarce commodity.

Beyond their scarcity, though, the transfusion of these products comes at a cost, and Table 2 outlines various blood products used to treat coagulopathy, their per unit expense, and the overall cost to the U.S. healthcare system of transfusion of these units, roughly estimated at 1.4 billion dollars. With estimates that 30% of plasma transfusions (72, 73) and 75% of platelet transfusions (74) are inappropriate, reducing transfusions to this degree has the potential to save over $850 million in reimbursed costs, a 64% reduction.

In addition to blood product usage, PCC, in combination with Vitamin K, has been shown to be a swift and effective means of reversal of warfarin-induced coagulopathy, and is the recommended agent for rapid reversal in the ACCP guidelines (75). The EPAHK study demonstrated a two-fold decrease in seven-day mortality in warfarin-treated patients with active hemorrhage from a variety of sites (gastrointestinal, intracranial, muscular, and others) treated with PCC and vitamin K within eight hours of emergency department admission (76). At $5,080 for a single dose to an 80-kg patient, the cost of administration is not inconsequential though, and Desmettre et al. have demonstrated that even in the setting of established guidelines, PCC is administered correctly and for appropriate reasons 30-40% of the time (77). Thus, improved education or restrictions on ordering may be necessary to prevent incurring excessive costs.

Treating Coagulopathy Leads to Adverse Reactions

Administration of blood products and any pharmaceutical agent for the correction of coagulopathy has the potential to generate an adverse reaction in the recipient. While many of these reactions are mild, like a fever or rash, they can be severe and include anaphylaxis and induce cardiopulmonary arrest. In plasma transfusions, the rates of all reactions are reported to occur between 1 in 591 and 1 in 2,184 transfusions, and typically, the offending protein or antigen is not identified (78). Platelet-associated reactions are similar in scope and in the uncertainty of their etiology; however, they occur more frequently, with between 1.6 and 30% of platelet transfusions resulting in an adverse response (79). Age of the platelet unit has been shown to influence this, with units aged 3 or more days showing a significant increase in adverse reactions (79). The processed PCC appears to be less likely than plasma to generate reactions; however, it is important to note that PCC preparations may contain heparin, and thus place patients at risk for the development of Heparin-Induced

Thrombocytopenia (HIT) (80). Both minor and severe tranexamic acid (TXA) reactions have also been reported; however, these appear to be rare (81).

In plasma and platelet transfusions, the presence of microparticles may be responsible for commonly seen reactions. These heterogeneous vesicles, derived from portions of cell membranes, are shed both physiologically and pathologically during inflammation, coagulation, complement activation, and shear stress (82). Germane to this discussion is that microparticles are clearly generated during component preparation, and their numbers increase during the storage of plasma, platelets, and cryoprecipitate as the storage duration increases (82, 83). Certain microparticles are known to be associated with febrile transfusion reactions, with Soluble CD40 ligand (sCD40L or CD154) and OX40 ligand both implicated in these processes (84).

Treating Coagulopathy Leads to Immune Dysfunction

Both the transfusion of blood products and the administration of medications may trigger dysfunctional immune responses. While a complete recounting of these immune responses is beyond the scope of this discussion, a brief treatment of the major immune consequences brought on by treatment of coagulopathy is provided.

Transfusion of any blood product has the potential to result in transfusion-related acute lung injury (TRALI). TRALI is the leading cause of transfusion-related mortality, and results from one of two mechanisms: 1) Non-antibody mediated, resultant from the transfusion of stored cell-containing blood products; and, 2) Antibody mediated, in which donor antibodies are passively transfused (85). The end result of either is recipient neutrophil activation, disruption of the pulmonary endothelium, fluid leak, and pulmonary edema progressing to acute lung injury (86). Plasma and Platelet transfusions are both associated with increased risk of TRALI relative to red blood cell transfusion (87). Utilizing patients receiving only red blood cell (RBC) transfusion as the index population, the risk of TRALI is increased 89% in patients receiving only plasma and 87% in patients receiving only platelets. Transfusing plasma and platelets together increases this risk over index a striking 256%.(87). Microparticle transmission may play a significant role in TRALI development. Khan and colleagues have shown that platelet concentrates involved in TRALI have significantly higher sCD40L levels than uninvolved units, and that sCD40L triggering of CD40 on recipient neutrophils primes PMN oxidase, leading to pulmonary endothelial cytotoxicity (83).

Transfusion-related immune modulation (TRIM) is a separate entity characterized by transfusion-mediated depression in monocyte and cytotoxic T cell activity while increasing suppressor T cell activity (88). Plasma administration has been shown to increase TNF-α and IL-10 production while decreasing endotoxin-mediated TNF-α release in an *in-vitro* transfusion model (89), possibly due to the presence of passively transfused Th2 cytokines (90). The clinical consequences of plasma-related TRIM include an increased incidence of nosocomial infections, sepsis, and multiple organ failure (91, 92). Platelet transfusion has been shown to result in TRIM through a different mechanism, with soluble MHC Class I molecules leading to a reduction of immune response to foreign antigens in a murine model

(93). This may contribute to the growth and metastasis of malignancies through a reduction in immune surveillance (94).

The antifibrinolytic medications TXA and ε-aminocaproic acid (EACA) pose a theoretical risk of immune modulation as well. By preventing the conversion of plasminogen to plasmin, fibrinolysis is inhibited; however, an additional downstream effect is a reduction in conversion of C1 to C1a and C3 to C3a in the complement cascade. Whether this translates to downstream immune dysfunction is unclear. Later, et al. showed that in patients undergoing cardiac surgery, patients receiving TXA and EACA showed less upregulation of pro-inflammatory genes and more upregulation of anti-inflammatory genes relative to patients not receiving these medications (95); however, they found no effects on cytokine or growth factor concentrations (96). Lewis and colleagues examined this issue retrospectively in military trauma patients; their results demonstrated no increased risk for infection, and further showed no decrease in time to infection in patients receiving TXA relative to those who had not, suggesting that early immune suppression in TXA-treated patients is not present (97). The ongoing Tranexamic Acid Mechanisms and Pharmacokinetics in Traumatic Injury (TAMPITI) trial is specifically focused on downstream immune effects following TXA administration, and should shed more light on this issue (98).

Treating Coagulopathy Doesn't Work

In spite of our continued use of blood products to treat coagulopathy, the evidence for this practice is limited. There are a number of excellent systematic reviews and meta-analyses on this subject, as well as emerging data to suggest that utilization of blood products is wasteful. A brief review of these data are included here.

While FFP has been used to treat coagulation abnormalities stemming from a number of disease states, this appears to be frequently ineffective. In ten randomized, controlled trials (RCTs) inclusive of seven prophylactic and three therapeutic studies, no significant benefits were seen in either transfusion requirements or coagulation test abnormalities among patients with hepatic dysfunction treated with FFP transfusion (99). In cardiac surgery, 19 RCTs (15 prophylactic, four therapeutic) have been completed, and have shown no differences in 24-hour blood loss among patients receiving or not receiving FFP (99). In warfarin reversal, FFP has been shown in five RCTs with 227 participants to be superior to Vitamin K at correction of INR at six hours following treatment; however, beyond this point, no differences are identified in degree of correction, or in overall mortality (99). In patients with severe traumatic brain injury and no history of coagulopathy, Etemedrezaie et al randomized 90 patients to either prophylactic FFP or saline control, finding that FFP patients showed an increase in delayed intracranial hematoma, and an overall increase in mortality (63 vs. 35%) (100).

Platelets fare no better than FFP in correction of coagulation abnormalities. In hypoproliferative thrombocytopenia, four RCTs inclusive of over 1,000 patients show no differences in all-cause or bleeding-related mortality between patients transfused platelets and those not receiving platelets (101). For procedural purposes in critical care units, there appears to be no benefit to prophylactic platelet transfusion for central venous catheter placements, thoracentesis, or paracentesis in thrombocytopenic patients(102). Providing

cardiac surgical patients with platelets prophylactically is associated with an increase in mortality (101). Patients receiving platelets for both traumatic and non-traumatic mechanisms of intracranial hemorrhage show no improvement in mortality (101); this has recently been demonstrated even in the setting of antiplatelet therapy with clopidogrel/prasugrel in the multicenter PATCH trial, with patients receiving platelets showing a greater rate of death or dependency three months following cerebrovascular accident (103).

Summary

At some point in the future, targeted therapies may be available for the treatment of pathologic coagulopathy, and this would have the potential of providing benefit without substantial risk. Unfortunately, that day has not yet arrived, and we are left with the imperfect modalities of blood product transfusion and broad pharmacotherapy for the treatment of coagulopathy which at this point remains a biomarker of severe injury and hemorrhagic shock. While use of these therapies in patients with active impairment of clotting and the subsequent effects (such as active hemorrhage) is warranted, treating disturbances in coagulation without just cause is clearly not; those caring for the critically ill should be aware of the cost, risks, and ineffectiveness of this strategy and act accordingly by not intervening. Perhaps the most important limitation regarding the current debate is the lack of an appropriate definition of coagulopathy. The lack of the ability to ‘define’ coagulopathy in sepsis and trauma is reflective of the heterogeneous nature of the disease process, with multi-factorial contributions from numerous cell types. Although individual components of these changes may be identified, their interrelatedness is unexplored. Certainly coagulopathy is no one ‘thing’ but rather a spectrum representing components of normal physiologic response, potentially pathological over or under activation of critical pathways (such as fibrinolysis), and coagulopathy is highly subject to alteration by resuscitation. Lumping the major components discussed above into one term, coagulopathy, is likely inherently flawed. Compounding these uncertainties is the lack of a ‘gold standard’ to measure coagulopathy; undoubtedly, the use of conventional coagulation testing designed as plasma based assays to monitor anticoagulation therapy is inadequate. Despite the profound noise in the system, the last decade has seen remarkable advances, perhaps in small steps, towards understanding the disturbances seen in coagulation associated with critical illness. As improved monitoring strategies emerge and are better understood (such as thromboelastography), promising clinical therapeutics are unveiled (such as tranexamic acid), and unique endotypes of coagulopathy associated with diseases such as trauma and sepsis are recognized, the ability to tease through the complexity may perhaps, emerge. For this reason, this remains an active and exciting area of research clouded by extraordinary complexity and uncertainty.

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Table 1
Anticoagulation effects on mortality in DIC

	APACHE II <20 (n=317)	APACHE II 20-30 (n=511)	APACHE II >30 (n=317)
Mortality without anti-coagulation (anti-thrombin +/- recombinant human thrombomodulin) (%) Adjusted OR	28.3 1.00	47 1.00	64.5 1.00
Mortality with anti-coagulation (anti-thrombin +/- recombinant human thrombomodulin)(%) Adjusted OR (95% CI)	21.8 0.64 (0.34-1.22)	35.5 0.52 (0.33-0.82)*	61.3 0.75 (0.43-1.28)

Mortality rates and adjusted odds ratio for death comparing patients with and without anticoagulation in overt DIC (defined as JAAM score ≥4 and ISTH score ≥5) in the J-SEPTIC DIC study.

Table 2

Costs and Reimbursements Associated with Plasma, Platelet, and Cryoprecipitate Transfusions in the United States, 2011

Type of Unit	Cost per Unit	Reimbursement per Unit	Number of Units	Cost	Reimbursement
Fresh Frozen Plasma*	$56.08	$73.15	3,882,000	$217,702,560	$283,968,300
Apheresis Platelets	$535.17	$538.51	1,970,000	$1,054,285,000	$1,060,865,000
Cryoprecipitate	$62.41	$50.41	1,094,000	$68,276,540	$55,148,540
Total				$1,340,264,100	$1,399,981,840

*Plasma units range in cost between $56.08 (frozen within 24 hours) and $57.91 (frozen within 8 hours)