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Practical understanding of hemostasis and approach to the bleeding patient in the OR

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Introduction

Coagulation and inflammation are biologic damage response systems activated and amplified following tissue injury. Although they were once thought to be separate and distinct processes, we now know that they are intrinsically linked and interactive systems.[1]

Bleeding, thrombosis and maladaptive inflammatory responses are major causes of perioperative morbidity and mortality for trauma and “non-trauma” patients.[2-4] Thus, coagulation and inflammation warrant serious consideration by all who care for surgical patients. New information regarding care of the bleeding trauma patient have led us to revisit our core concepts of caring for other patients with massive bleeding as well.

In this article we will briefly review the different models of coagulation, discuss management of the acute coagulopathy associated with severe trauma and relate that to the care of other bleeding patients.

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Classical coagulation cascade

Observation leading to discovery—Astute physicians, noting unusual bleeding tendencies in their patients, in collaboration with brilliant scientists deduced the proteolytic activation of zymogens in plasma leading to fibrin formation. This “Waterfall/Cascade” described more than fifty years ago, has been the basis for testing and monitoring anticoagulant effects of various medications for decades.[5] (Figure 1)

Beyond the “Waterfall/Cascade”

Although the intrinsic and extrinsic pathways seem somewhat complex, they were never thought to be the full explanation of human hemostasis. This classical model addresses plasma and the factors within it. It does not include considerations of the dynamic cellular processes that are now known to play major roles in procoagulant and anticoagulant physiology. The newer “cellular model” takes some of these into consideration. Thrombus formation within this model is typically divided into three overlapping phases: initiation, amplification and propagation. (Figure 2)

Regulation—In its normal state, blood within the circulatory system remains in a liquid state, freely flowing throughout the body. Excessive and uninhibited procoagulant and inflammatory processes with concomitant lack of tissue perfusion lead to multi-organ failure (MOF) and death. Thrombosis and inflammation must be localized to the site of injury, thus the processes are regulated in several ways. Localization occurs primarily by endothelial processes, flow dilution of factors and active fibrinolysis. Inhibitory processes within the coagulation system play major roles in regulation of thrombosis. (Table 1)[6]

Endothelial roles in regulation—The endothelium has been found to be intrinsically involved in regulation of coagulation in many ways. The endothelium first comes into play with vasoconstriction as an initial defense against blood loss. Endothelium is known to express antithrombin, thrombomodulin, tissue factor pathway inhibitor (TFPI), and tissue factor among other roles. (List 1)[7, 8]

Importance of the endothelial glycocalyx—The endothelial glycocalyx is now known to be extremely important in both localizing thrombosis and preventing inappropriate thrombosis, in preventing tissue edema, and in modulating immune activation. If this luminal anticoagulant covering is damaged, endothelial activation of coagulation and inflammation occur. This is considered one of the important mechanisms of MOF from trauma at distant sites.[9-11]

Continued evolution of our understanding—We are continuing to develop our understanding of many aspects of plasma, vascular and extravascular processes important in coagulation. TF expression and its regulation, flow dynamics, shear stress related conformational changes, turbulence, spatial and temporal considerations and other more basic processes continue to be elucidated. One recent example is the role of the growth arrest specific-6 (Gas6) protein in expression of TF by endothelial cells. The vitamin-K dependent protein Gas6 binds to endothelial Tyro, Axyl, Mer (TAM) receptors inducing

vascular tissue factor expression. This tissue factor then binds factor VIIa initiating coagulation.[12, 13]

Trauma/Inflammation/Coagulopathy

It follows that tissue damage sufficient to require hemostasis would have subsequent healing promoted by protection from bacterial invasion, clearance of cellular debris and other inflammatory responses. Therefore it's not surprising that coagulation and inflammation are linked. (List 2)[1] Many components of one system affect processes within the other and they also share many regulatory processes.

Immune response to injury—The inflammatory response is absolutely necessary for healing and recuperation following injury, but if not appropriately balanced and controlled, may lead to life threatening complications of its own. Excessive and prolonged pro-inflammatory response following trauma has been associated with multi-organ failure and death. [14, 15]

The neutrophils and macrophages of the innate immune system carry the majority of the responsibility for tissue defense and clearance of cellular debris following traumatic tissue injury. Excessive response however leads to the systemic inflammatory response syndrome (SIRS) and sepsis in a manner surprisingly similar to other causes. [4, 16-18] Xiao, et al demonstrated the remarkably uniform nature of inflammatory responses to bacterial pathogens, burns and trauma at a transcriptomic and genomic level. They also showed that pro-inflammatory and anti-inflammatory processes both begin immediately following tissue injury.[4]

Coagulopathy from excessive, dysregulated inflammatory response is well documented in SIRS and sepsis. More recently, its importance in trauma-induced coagulopathy (TIC) has become increasingly evident.[19] Additional support for this concept came recently from a secondary analysis of the Inflammation and the Host Response to Injury Large Scale Collaborative Program (Glue Grant; <https://www.gluegrant.org/>). Neal, et al revealed an association between prehospital non-steroidal anti-inflammatory (NSAID) use and a significant reduction in TIC.[20]

A Mechanism of tissue injury induced inflammation—Tissue injury causes the release of intracellular components into the circulation at concentrations much higher than is seen with programmed cell death. Much like the pathogen associated molecular patterns that cause inflammatory response to bacterial invasion, intracellular debris may serve as damage associated molecular patterns (DAMPs), or “alarmins”.[21] Mitochondrial DNA, with significant bacterial similarity, is one such DAMP.[22]

Pattern recognition receptors, such as toll-like receptors and the receptor for advanced glycation end products, recognize these DAMPs and initiate cytokine production and inflammatory response. Of note, additional evidence of the interdependence of coagulation and inflammation is seen in the fact that DAMPs cause direct activation of coagulation. [23]

Severity of tissue injury is associated with proportional increases in proinflammatory markers, including cytokine IL-6. Increased IL-6 levels from surgery or trauma are also associated with activation of coagulation, endocrine response and post-surgical complications.[24-31]

Importance of Trauma Induced Coagulopathy—Coagulopathy has long been recognized as a lethal component of trauma. When combined with acidemia and hypothermia it forms the “lethal triad”. Our understanding of the coagulopathy associated with trauma has progressed over the years. The dilution of factors and platelets secondary to resuscitation and hypothermia that was recognized years ago is still considered an important factor. In fact, it should be considered in any “massive resuscitation”.

However, research into trauma induced coagulopathy (TIC) revealed a severe coagulopathy (demonstrable before resuscitation) that had not been previously clinically appreciated. TIC is now known to be a consequence of severe tissue injury and shock-induced hypoperfusion with other contributing factors. (List 3)[32, 33] In order to have a significant impact upon this problem, early identification of patients at risk and prompt treatment is extremely important.

Management Goals

Newer models of treatment for trauma resuscitation—For decades, crystalloid based resuscitation of the severely injured patient was standard, but this practice is increasingly being re-evaluated and modified. Large volume crystalloid resuscitation leads to tissue edema thus worsening tissue oxygenation and perfusion. This worsens a pathological cycle of hypoperfusion, tissue injury and inflammatory complications. (Figure 3)

Our current practice of goal directed resuscitation aims to break this cycle utilizing a technique that has been referred to as “damage control resuscitation” (DCR). (List 4) DCR describes an approach to resuscitation that may be broken down into two major components: hypotensive and hemostatic resuscitation. It is usually combined with damage control surgery (DCS) in an attempt to improve the survival of severely traumatized patients.

Time is of the essence when treating a bleeding patient and temporary control via direct pressure or tourniquet is very important. The very best resuscitation with fractionated blood components still falls short of providing the function of native blood with its own inflammatory mediators, antigens and coagulation components. Herein lies the importance of direct control of bleeding via surgical and topical therapies aided by DCR techniques including hypotensive resuscitation: it helps maintain the patients intrinsic blood volume.

Identification of the need for massive transfusion—Certain clinical indicators and lab values have been demonstrated in trauma patients to be associated with a need for massive transfusion (MT). These have been assimilated into scoring systems that may be employed as triggers for initiating a massive transfusion protocol (MTP). If a patient meets the appropriate criteria, the MTP should be initiated immediately to avoid lost opportunity

for corrections.[32] There are common factors associated with a need for MT and a simple clinical scoring system is available that aids in identifying trauma patients at high risk for MT. (Tables 2 and 3)[32, 34]

Two models of resuscitation—There are two competing models that aim to best implement the concepts of DCR. A protocol driven model that utilizes a ratio (e.g., 1:1:1=red blood cells (rbc): fresh frozen plasma (ffp): platelets) of available blood components vs. a point of care (POC) coagulation testing model that utilizes rapid coagulation testing and specific therapy (including concentrated factors) for abnormalities that are discovered. There are specific rationales and concerns associated with each of these approaches. (Table 4)

Point of care coagulation testing—In a situation of rapid exsanguination, the patient's clinical status continues to change very rapidly and it takes far too long to receive the results from traditional coagulation testing to provide direction for current treatment.[35] In this situation, the patient's clinical status continues to change very rapidly. Within the hour, or more that it takes for the information to return, the patient has continued to bleed and may have received several procoagulant therapies.

Traditional coagulation testing is also considered unreliable in characterizing TIC. Prothrombin time (PT), International normalized ratio (INR) and activated partial thromboplastin times (aPTT) all utilize plasma samples devoid of blood's cellular components that play major roles in vivo. These tests also do not consider clot stability, fibrin functionality or fibrinolysis.[36]

The recently published Society of Thoracic Surgeons Blood Conservation Guideline Task Force recommendations (2007) and the update (2011) include POC coagulation testing in their recommendations.[37] Also, POC testing is featured prominently in the European guidelines regarding “Management of bleeding and coagulopathy following major trauma” updated in December of 2013.[38]

Rapid viscoelastic and platelet function testing is increasingly proving beneficial in this area. Thromboelastography (TEG, Haemonetics Corporation, USA) and rotational thromboelastometry (ROTEM, Pentapharm, Germany) both utilize whole blood samples to help rapidly evaluate coagulation processes including blood cellular contributions and fibrinolysis.

How viscoelastic tests help

Normal TEG/ROTEM—One of the strengths of TEG/ROTEM lies in their strong negative predictive power.[39] In other words, if the TEG/ROTEM is normal, observed clinical bleeding is almost certainly not due to coagulopathy, and is more likely due to uncontrolled surgical bleeding or “suture” deficiency. (Figure 4A) The source should be discovered and controlled if discreet. Topical prothrombotic agents should be strongly considered. Interventional radiological procedures may be necessary and should be considered as well.

Abnormal TEG/ROTEM—Different components of the TEG/ROTEM reveal different defects in hemostasis. Inadequate factor, fibrinogen, and platelet function all show different TEG/ROTEM abnormalities, as does hyperfibrinolysis. Abnormal results in the TEG/ROTEM help direct therapy by indicating the source of the coagulation dysfunction.[39] Prolonged coagulation initiation (R/CT), decreased kinetics of formation (k/CFT), inability to attain an adequate maximum strength (MA/MCF) and excessive fibrinolysis (LY30/Li30) each has a specific associated therapy. (Figure 4B)

Just as traditional coagulation testing does not reveal the entire in vivo clotting process, viscoelastic testing is limited as well. Unfortunately, it does not reflect vascular (glycocalyx, endothelium, vessel wall, etc.) or extravascular contributions to clotting. Also, the activators utilized in the testing process cause generation of thrombin. As such, TEG/ROTEM may not identify problems associated with platelet dysfunction secondary to antiplatelet therapies (aspirin, clopidogrel, etc.) or associated with trauma.[40, 41] Specific platelet function testing is usually performed by other methods, as discussed below.

Platelet testing—Turbidimetric platelet aggregometry is the trusted “gold standard” assay for platelet function, however some drawbacks, including long “turn-around” time, render it rather useless in the treatment of acute massive bleeding however. Newer tests, including viscoelastic platelet mapping, impedance aggregometry (IA) and platelet function analysis offer rapid POC assessment of platelet function.

Platelet mapping—TEG PlateletMapping assay allows the evaluation of platelet function as it relates to antiplatelet therapy. It reports the percentage of inhibition or aggregation compared to the patient's uninhibited maximum response. PlateletMapping shows promise, however, this function is not a simple test, not a standard TEG test and currently unavailable on ROTEM. Also, TEG platelet mapping utilizes three channels thus requiring two machines.

Impedance aggregometry—IA testing (Multiplate, Roche, Switzerland) offers rapid POC platelet function testing. Impedance increases as platelets aggregate upon the electrodes in the sample. IA is capable of determining platelet functional defects related to vascular injury (collagen) and antiplatelet therapy (ADP) among others, within minutes.

Using IA, Kutcher et al. recently revealed clinically significant defects in platelet functionality associated with trauma.[41] Trauma induced platelet dysfunction was present despite adequate quantitative platelet values (and other traditional coagulation tests) and was found predictive of both early and late mortality.

IA and ROTEM are components of the POC testing guided approach to TIC since both tests offer results within a few minutes and evaluate different aspects of coagulopathy. IA is currently utilized for clinical testing in Europe but is currently unavailable in the United States, except for use in research. A somewhat limited version has recently received FDA approval for clinical use and may be available by the end of 2014.[42]

Fibrinolysis testing—Traditional testing for fibrinolysis includes quantification of the cross-linked fibrin degradation product D-dimer and the euglobulin clot lysis time (ECLT). D-dimer testing results are typically available in one to two hours. Elevated D-dimer is non-specific as it may be associated with many different entities including venous thromboembolism, syncope, heart failure, trauma and cancer.[43] The ECLT is labor intensive and takes three to six hours to complete, and in many laboratories is thus routinely processed once each morning. TEG/ROTEM accurately reveals significant hyperfibrinolysis within 30 minutes from clot initiation (ROTEM) or from maximum amplitude (TEG).

Role of traditional coagulation tests—Care should be exercised when interpreting any lab data, including viscoelastic tests, thus additional testing is warranted to provide confirmatory and complementary data. Traditional screening tests, such as aPTT and PT/INR along with quantitative fibrinogen and platelet values help to assure correct interpretation and performance of advanced tests.

A combined approach to resuscitation

In resuscitation from acute massive hemorrhage, a combination of the two models (protocol-driven and point-of-care-testing –driven) may provide improved results. This combined model may address limitations in each individually. (Figure 5) The recently updated European guidelines that promote point-of-care coagulation testing also support this combined approach. It states:

“Recommendation 26 We recommend the initial administration of plasma (fresh frozen plasma (FFP) or pathogen-inactivated plasma) (Grade 1B) or fibrinogen (Grade 1C) in patients with massive bleeding.

If further plasma is administered, we suggest an optimal plasma:red blood cell ratio of at least 1:2. (Grade 2C)

We recommend that plasma transfusion be avoided in patients without substantial bleeding. (Grade 1B)”[38]

In this manner, early identification of a serious clinical problem, immediate institution of therapy, monitoring of coagulation changes, and rapid adjustment of treatment is possible. Benefits to the patient would include treatment of the major components of the lethal triad, prevention of an escalating problem of inflammation with minimization of total blood product utilization and their inherent risks.

DCR in non-trauma patients

Surgical hemorrhage as trauma induced bleeding—As previously noted, tissue injury when combined with hemorrhagic shock initiates a massive inflammatory response capable of proceeding to TIC, SIRS, MOF and death. Tissue injury of sufficient magnitude, regardless of its source, including surgery, along with hemorrhagic shock is sufficient to enact this scenario.

Massive hemorrhage is a major cause of death following severe trauma. It's also associated with significantly increased mortality from surgery.[44, 45] When bleeding continues or is acutely intense enough to warrant consideration of treatment with blood components or pro-coagulants, rapid assessment of coagulation is warranted. Often, blood products are utilized despite a lack of understanding of the benefits, risks, options and costs involved.[46]

Coagulopathy—While the majority of intraoperative hemorrhage is associated with surgical technique or “suture deficiency” requiring direct control, coagulopathy resulting in additional microvascular bleeding may develop and contribute to the clinical challenge.[44] TIC develops in association with a maladaptive protein-C response, massive inflammatory response to DAMPs and tissue hypoperfusion; in analogous fashion, coagulopathy from “surgical trauma” may develop. As evaluated by TEG results, early administration of FFP and platelets along with red blood cells has been shown to maintain coagulation capacity in a variety of massively bleeding patients.[47]

Predicting hemorrhage—In the OR, the likelihood of massive hemorrhage is associated with the type or complexity of the procedure. Cardiac, major vascular, trauma, major orthopedic, organ transplantation and complex oncological procedures are all likely candidates for increased risks of operative bleeding. Patients with a higher likelihood of perioperative hemorrhage include those with incompetent coagulation systems (intrinsic or iatrogenic), and co-morbidities characterized by diminished physiologic states (e.g., malnutrition, chronic steroid use, advanced age, ASA III-IV, hepatic or renal insufficiency, etc.).[37, 48]

Blood conservation—In 2007, the Society of Thoracic Surgeons Blood Conservation Guideline Task Force made recommendations regarding blood conservation for cardiac surgery. A planned revision, incorporating newer information was published in 2011. These guidelines contain considerations appropriate for other procedures associated with bleeding risk as well. (List 5)[49]

Coagulation testing for perioperative massive hemorrhage—Advanced POC testing, including viscoelastic and rapid platelet function tests, would be best suited to provide results rapidly enough to help evaluate coagulopathy in massive hemorrhage. In a prospective, randomized study, Weber, et al. evaluated POC testing (ROTEM and IA) in patients clinically considered to be coagulopathic after complex cardiac surgery. They performed a planned interim analysis and terminated their study early because of a significantly decreased erythrocyte transfusion rate in the POC cohort. Several secondary outcome parameters, including decreased FFP and platelet transfusion rates, length of ICU stay and 6 month mortality rates were also found to be lower in the POC group.[50]

Trigger of MTP—As discussed before, in trauma, certain clinical indicators and lab values have been developed into triggers for initiating a massive transfusion protocol. This is not the case for operative procedures. Resuscitation often proceeds as indicated by estimated blood loss and hemodynamic instability. Uncontrolled bleeding resulting in hypotension should be considered a trigger, as well. As we understand the mechanisms of TIC more

fully, we realize that emphasis should be placed upon maintenance of coagulation capacity in massive hemorrhage as well as in TIC.

Application of DCR methods to non-trauma patients

Massive hemorrhage, regardless of the cause, must be treated rapidly with the same basic goals of trauma resuscitation.

- Rapid surgical control of bleeding cannot be overemphasized, and its absence cannot be overcome with medical treatment.
- Identify patients requiring “massive transfusion” as early as possible. Inability to directly control the source of bleeding due to a cryptic source, anatomic challenge, etc. leading to hemorrhagic shock is very similar to the sequence in the development of TIC. Clear and direct communication between the surgical and anesthesia teams is paramount. Early recognition of poorly controlled bleeding allows rapid conversion to more appropriate resuscitation methods.
- Promptly initiate an appropriate hemostatic resuscitation (MTP).

Baseline “stat labs” and if available POC testing should be initiated. Early considerations include:

- Adequate intravenous access for resuscitation is critical.
- Arterial pressure monitoring is very helpful but should not delay therapy. Waveform analysis and changes associated with therapy provide rapid information regarding contractility and volume status, and blood sampling for serial labs is simplified.
- Tranexamic acid has proven beneficial in trauma and other settings.[51]
- Desmopressin (DDAVP) induces endothelial release of factor VIII and von Willebrand factor, and improves primary hemostasis in settings of von Willebrand's disease, anti-platelet therapy, acidemia and hypothermia.[38]
- Excessive crystalloid-based resuscitation is detrimental.
- Early administration of available replacement therapy is indicated. FFP, fractionated products, fibrinogen concentrates, cryoprecipitate, platelets, etc. should be instituted as indicated to maintain coagulation function. In this specific subset of patients, much greater use of blood products and other procoagulants is seen when therapy is delayed, and thus early intervention helps decrease utilization of these resources.
- Improve/maintain tissue perfusion.
 - Adequate tissue perfusion promotes correction of acidemia.
 - Base excess and lactate levels at baseline and sequentially, helps monitor adequacy of perfusion.
 - Maintenance of the microcirculation with appropriate resuscitation and support of cardiac output when needed, helps prevent global inflammatory

activation, hopefully decreasing the likelihood of progression to MOF and worse.

- Norepinephrine may be utilized as bridging therapy, but continued use of vasoconstricting medications may be counter-productive in leading to worsening global tissue perfusion, thus promoting acidemia. However, if volume resuscitation alone fails to attain adequate blood pressure due to other factors, norepinephrine infusion may indeed need to be continued.
- Permissive hypotension is considered beneficial in uncontrolled bleeding.
 - Prevention of the excess bleeding associated with increased blood pressure must be balanced with the need for critical organ perfusion. In a non-vasoconstricted patient, tissue perfusion is typically adequate with minimal adverse effect. Regional perfusion to critical organs in the setting of comorbidities is a concern, however. Specific limitations to the degree of hypotension that should be permitted exist in the setting of traumatic brain injury: recommendations for no less than a systolic blood pressure of 90 mmHg (American Association of Neurological Surgeons)[52] and a mean arterial pressure of 80 mmHg (European guidelines)[38] have been established.

*NOTE: Intentional hypotension should be discontinued after surgical control of bleeding is attained in order to improve tissue perfusion. There is also concern that in an artificially hypotensive state, vascular bleeding can be masked. For this reason, blood pressure should be allowed to rise to the levels expected postoperatively, prior to wound closure. This allows visual confirmation of hemostasis and may prevent some immediate postoperative “re-bleeding” and emergent re-entry.

- Minimize crystalloid resuscitation

Restricting crystalloid administration minimizes hemodilution of coagulation factors, decreases tissue edema and avoids excessive chloride load.

- Treat/prevent hypothermia

All resuscitation fluids should be warmed where appropriate and active warming devices should be utilized.

- Correct electrolyte abnormalities

In the setting of massive resuscitation, electrolyte abnormalities are common. Administration of citrate containing blood products, along with consumption of calcium during clotting processes often leads to decreased ionized calcium levels that should be monitored and replaced.

Conclusion

Coagulation and inflammation are two major biologic response systems following tissue trauma. A complex interaction between these two systems following severe injury may

result in coagulopathy and an increased likelihood of poor outcomes. Improved understanding of the bleeding seen in severe trauma settings has informed our treatment of poorly controlled bleeding in the operating room. Massive hemorrhage is a serious and rapidly changing situation associated with significant increase in mortality rates. We recommend that a multidisciplinary blood management team establish rapid response systems and algorithms to facilitate the clinical response to massive hemorrhage.

Identification of high-risk patients and procedures allows pre-procedure consideration and preparation promoting good outcomes. Once high risk is identified, concepts of blood product conservation should be utilized before during and after the procedure. Rapid, acute hemorrhage is not immediately reflected in decreased hemoglobin/hematocrit nor is acute coagulopathy able to be characterized by standard coagulation tests. Appropriate therapy must be rapidly instituted in order to avoid a “bloody vicious cycle” of bleeding and coagulopathy. In the setting of massive hemorrhage where coagulopathy may be contributory, damage control resuscitation concepts should be utilized. POC testing is capable of guiding therapy in this dynamic situation, and we recommend blending protocol-driven and testing-driven approaches to the bleeding patient. New information and capabilities arise continuously therefore we must continue to stay abreast of current recommendations and developments.

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References

1. Petaja J. Inflammation and coagulation. An overview. *Thromb Res.* 2011; 127 Suppl 2:S34–7. [PubMed: 21193113]
2. Adams GL, et al. The balance of thrombosis and hemorrhage in surgery. *Hematol Oncol Clin North Am.* 2007; 21(1):13–24. [PubMed: 17258115]
3. Desai KH, et al. Dissecting inflammatory complications in critically injured patients by within-patient gene expression changes: a longitudinal clinical genomics study. *PLoS Med.* 2011; 8(9):e1001093. [PubMed: 21931541]
4. Xiao W, et al. A genomic storm in critically injured humans. *J Exp Med.* 2011; 208(13):2581–90. [PubMed: 22110166]
5. Davie EW. A brief historical review of the waterfall/cascade of blood coagulation. *J Biol Chem.* 2003; 278(51):50819–32. [PubMed: 14570883]
6. Adams RL, Bird RJ. Review article: Coagulation cascade and therapeutics update: relevance to nephrology. Part 1: Overview of coagulation, thrombophilias and history of anticoagulants. *Nephrology (Carlton).* 2009; 14(5):462–70. [PubMed: 19674315]
7. van Hinsbergh VW. Endothelium—role in regulation of coagulation and inflammation. *Semin Immunopathol.* 2012; 34(1):93–106. [PubMed: 21845431]
8. Rivera J, et al. Platelet receptors and signaling in the dynamics of thrombus formation. *Haematologica.* 2009; 94(5):700–11. [PubMed: 19286885]
9. Mulivor AW, Lipowsky HH. Inflammation- and ischemia-induced shedding of venular glycocalyx. *Am J Physiol Heart Circ Physiol.* 2004; 286(5):H1672–80. [PubMed: 14704229]
10. Chappell D, Westphal M, Jacob M. The impact of the glycocalyx on microcirculatory oxygen distribution in critical illness. *Curr Opin Anaesthesiol.* 2009; 22(2):155–62. [PubMed: 19307890]

11. Torres LN, et al. Evaluation of resuscitation fluids on endothelial glycocalyx, venular blood flow, and coagulation function after hemorrhagic shock in rats. *J Trauma Acute Care Surg.* 2013; 75(5): 759–66. [PubMed: 24158192]
12. Foley JH, Conway EM. Gas6 gains entry into the coagulation cascade. *Blood.* 2013; 121(4):570–1. [PubMed: 23349372]
13. Robins RS, et al. Vascular Gas6 contributes to thrombogenesis and promotes tissue factor up-regulation after vessel injury in mice. *Blood.* 2013; 121(4):692–9. [PubMed: 23149844]
14. Gentile LF, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. *J Trauma Acute Care Surg.* 2012; 72(6):1491–501. [PubMed: 22695412]
15. Gando S, et al. Combined activation of coagulation and inflammation has an important role in multiple organ dysfunction and poor outcome after severe trauma. *Thromb Haemost.* 2002; 88(6): 943–9. [PubMed: 12529743]
16. Chow CC, et al. The acute inflammatory response in diverse shock states. *Shock.* 2005; 24(1):74–84. [PubMed: 15988324]
17. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. *Injury.* 2007; 38(12): 1336–45. [PubMed: 18048040]
18. Tsukamoto T, Chanthaphavong RS, Pape HC. Current theories on the pathophysiology of multiple organ failure after trauma. *Injury.* 2010; 41(1):21–6. [PubMed: 19729158]
19. Pierce A, Pittet JF. Inflammatory response to trauma: implications for coagulation and resuscitation. *Curr Opin Anaesthesiol.* 2014; 27(2):246–52. [PubMed: 24419158]
20. Neal MD, et al. Prehospital Use of Nonsteroidal Anti-inflammatory Drugs (NSAIDs) Is Associated With a Reduced Incidence of Trauma-Induced Coagulopathy. *Ann Surg.* 2014
21. Matzinger P. The danger model: a renewed sense of self. *Science.* 2002; 296(5566):301–5. [PubMed: 11951032]
22. Zhang Q, et al. Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature.* 2010; 464(7285):104–7. [PubMed: 20203610]
23. Esmon CT, Xu J, Lupu F. Innate immunity and coagulation. *J Thromb Haemost.* 2011; 9 Suppl 1:182–8. [PubMed: 21781254]
24. Pulicino EA, et al. The relationship between the circulating concentrations of interleukin 6 (IL-6), tumor necrosis factor (TNF) and the acute phase response to elective surgery and accidental injury. *Lymphokine Res.* 1990; 9(2):231–8. [PubMed: 1692598]
25. Yilmaz S, et al. Short period of preconditioning protects by decreasing the TNF-alpha and IL-6 values before laparoscopic surgery (a rat experiment). *Med Sci Monit.* 2010; 16(2):BR75–9. [PubMed: 20110913]
26. Hisano S, et al. IL-6 and soluble IL-6 receptor levels change differently after surgery both in the blood and in the operative field. *Cytokine.* 1997; 9(6):447–52. [PubMed: 9199879]
27. Uchida I, et al. An increase in circulating IL-6 levels correlates to endocrine response to abdominal surgery: preliminary report. *Nihon Geka Gakkai Zasshi.* 1991; 92(12):1726. [PubMed: 1667232]
28. Sanders J, et al. Higher IL-6 levels but not IL6 -174G>C or -572G>C genotype are associated with post-operative complication following coronary artery bypass graft (CABG) surgery. *Atherosclerosis.* 2009; 204(1):196–201. [PubMed: 18922529]
29. Sedlar M, et al. Older age and type of surgery predict the early inflammatory response to hip trauma mediated by interleukin-6 (IL-6). *Arch Gerontol Geriatr.* 2010; 51(1):e1–6. [PubMed: 19615763]
30. Tschoeke SK, et al. The early second hit in trauma management augments the proinflammatory immune response to multiple injuries. *J Trauma.* 2007; 62(6):1396–403. discussion 1403–4. [PubMed: 17563655]
31. Jiang J, et al. Kinetics of plasma cytokines and its clinical significance in patients with severe trauma. *Chin Med J (Engl).* 1997; 110(12):923–6. [PubMed: 9772403]
32. Maegele M, Spinella PC, Schochl H. The acute coagulopathy of trauma: mechanisms and tools for risk stratification. *Shock.* 2012; 38(5):450–8. [PubMed: 23042192]

33. Chambers LA, Chow SJ, Shaffer LE. 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):364–70. [PubMed: 21846911]
34. Nunez TC, et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma.* 2009; 66(2):346–52. [PubMed: 19204506]
35. Davenport R, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med.* 2011; 39(12):2652–8. [PubMed: 21765358]
36. Schochl H, et al. Early and individualized goal-directed therapy for trauma-induced coagulopathy. *Scand J Trauma Resusc Emerg Med.* 2012; 20:15. [PubMed: 22364525]
37. Society of Thoracic Surgeons Blood Conservation Guideline Task, F. Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline. *Ann Thorac Surg.* 2007; 83(5 Suppl):S27–86. [PubMed: 17462454]
38. Spahn DR, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care.* 2013; 17(2):R76. [PubMed: 23601765]
39. Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. *Anesth Analg.* 2008; 106(5):1366–75. [PubMed: 18420846]
40. McMichael MA, Smith SA. Viscoelastic coagulation testing: technology, applications, and limitations. *Vet Clin Pathol.* 2011; 40(2):140–53. [PubMed: 21446994]
41. Kutcher ME, et al. Characterization of platelet dysfunction after trauma. *J Trauma Acute Care Surg.* 2012; 73(1):13–9. [PubMed: 22743367]
42. FDA medical devices online database. 2014
43. Lippi G, et al. Causes of elevated D-dimer in patients admitted to a large urban emergency department. *Eur J Intern Med.* 2014; 25(1):45–8. [PubMed: 23948628]
44. Marietta M, et al. Pathophysiology of bleeding in surgery. *Transplant Proc.* 2006; 38(3):812–4. [PubMed: 16647479]
45. Marietta M, et al. Massive bleeding: Are we doing our best? *Transfus Apher Sci.* 2011; 45(3):287–90. [PubMed: 22071225]
46. Shander A. Financial and clinical outcomes associated with surgical bleeding complications. *Surgery.* 2007; 142(4 Suppl):S20–5. [PubMed: 18019945]
47. Johansson PI, et al. Transfusion packages for massively bleeding patients: the effect on clot formation and stability as evaluated by Thrombelastograph (TEG). *Transfus Apher Sci.* 2008; 39(1):3–8. [PubMed: 18583193]
48. Odumala AO, Ayekoloye CI, Packer G. Predictors of excessive blood loss during operative treatment of hip fractures. *J R Coll Surg Edinb.* 2002; 47(3):552–6. [PubMed: 12109609]
49. Society of Thoracic Surgeons Blood Conservation Guideline Task, F. 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. *Ann Thorac Surg.* 2011; 91(3):944–82. [PubMed: 21353044]
50. Weber CF, et al. Point-of-care testing: a prospective, randomized clinical trial of efficacy in coagulopathic cardiac surgery patients. *Anesthesiology.* 2012; 117(3):531–47. [PubMed: 22914710]
51. Ker K, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ.* 2012; 344:e3054. [PubMed: 22611164]
52. Brain Trauma, F. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma.* 2007; 24 Suppl 1:S7–13. [PubMed: 17511549]

Synopsis

Coagulation and inflammation are interlinked damage response systems. This understanding is an important basis for approaching hemostatic resuscitation of an exsanguinating patient. Newer, goal directed trauma resuscitation models should be considered when treating any massive hemorrhage in the operating room. Rapid, point of care coagulation testing may be the best tool for guiding therapy in this situation.

- Coagulation and inflammation are two major biologic response systems following tissue trauma.
- A complex interaction between these two systems following severe injury may result in coagulopathy and an increased likelihood of poor outcomes.
- Improved understanding of the bleeding seen in severe trauma settings has informed our treatment of poorly controlled bleeding in the operating room.
- Massive hemorrhage is a serious and rapidly changing situation associated with significant increase in mortality rates.
- Identification of high-risk patients and procedures allows pre-procedure consideration and preparation promoting good outcomes.

Figure 1. Waterfall cascade, the classical description of coagulation

Roman numerals indicate the numbered coagulation factors. When followed by an "a", they represent their active forms. TF=tissue factor, Ca⁺⁺=calcium.

STABLE THROMBUS

Figure 2. Cellular model of coagulation

This represents the three stages leading to thrombus formation within the cellular model of coagulation, including the contribution of platelets.

Figure 3. The pathological cycle of hypoperfusion, tissue injury and inflammatory complications
Tissue edema is worsened by aggressive crystalloid based resuscitation, thus propagating this cycle.

Figure 4A. Normal appearing TEG/ROTEM graph and parameters

The appearance of TEG and ROTEM graphs are quite similar yet with different nomenclature and lysis interval timing. TEG=thromboelastograph, TEG terms are: MA=maximum amplitude, α =alpha angle, R=reaction time, k=kinetics, LY30=lysis 30 minutes after MA. ROTEM=rotational thromboelastometry, MCF=maximum clot firmness, CT=clotting time, CFT=clot formation time, Li30=lysis index 30 minutes after CT.

Figure 4B. Treatments based upon areas of abnormal values

Abnormal results in different areas of the graph help direct therapy by revealing the problematic area within the coagulation system. As shown, there is overlap in the therapies indicated by certain abnormal results.

Figure 5. A combined resuscitation approach

Combining the two models of massive transfusion, a reasonable and effective strategy such as this may best address concerns raised by both.

Table 1
Effects of the main natural anticoagulant proteins on the coagulation cascade

The anticoagulant proteins listed on the left inhibit the corresponding items listed on the right.

	Inhibits
Antithrombin	Thrombin, FIXa, Xa, FXIa, FXIIa
Thrombomodulin	Fva, FVIIIa
Protein C	FV, FVIII
Protein S	FV, FVIII
Tissue factor pathway inhibitor (TFPI)	TF:FVIIa, FXa
Intact endothelial glycocalyx	Endothelial platelet bonding

Table 2
Major indicators of need for massive transfusion in trauma

These (and other) indicators have been utilized in different scoring systems to help predict the need for massive transfusion in trauma.

Clinical Indicators	Laboratory Indicators
Injury Severity Score > 15	Base Deficit < -6
Systolic Pressure < 90 mmHg	INR > 1.2
Temperature < 35.5°C	Hemoglobin < 11 g/dL
Heart Rate > 120 bpm	pH < 7.25
Positive FAST exam	
GCS <9	

Table 3**A Simple system to help predict massive transfusion needs in trauma**

The assessment of blood consumption (ABC) score utilizes readily available clinical indicators to help predict the need for massive transfusion in trauma.

Assessment of Blood Consumption (ABC) Score	
Penetrating Mechanism	1
Arrival Systolic Blood Pressure < 90 mmHg	1
Arrival Heart Rate > 120 /minute	1
FAST exam positive	1

Sum = 2 correctly classified 85% of massive transfusion patients.

Table 4
The two major models of trauma resuscitation

These models were developed based upon prior experiences and considerations within two different healthcare systems. Availability of testing and products is dissimilar as well.

Model	Rational	Concern	Location
Ratio driven protocol	<ul style="list-style-type: none"> Improved early survival in MT patients Early intervention decreases over-all transfusion requirements Rapid POC testing and concentrated products largely unavailable 	<ul style="list-style-type: none"> Morbidity and mortality associated with non-specific transfusion rationale Waste of pre-prepared blood products Cost of blood products 	United States
Point of Care Testing Protocol	<ul style="list-style-type: none"> Indiscriminant use of blood products is harmful Rapid POC testing allows specificity of therapy, including blood products 	<ul style="list-style-type: none"> Potential for delay in therapy and lost opportunity FFP contains some beneficial components not commercially available Cost of therapies 	Europe

List 1

Examples of endothelial interactions with coagulation

The endothelium interacts within the coagulation system via platelets, factors and fibrinolysis. This is a partial list of these interactions only and is not, by any means, considered exhaustive. ADAMTS-13= a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, Gas6=growth arrest specific 6 protein.

Platelet Interactions

Activation

Adhesion

Von Willebrand factor (vWF) production

ADAMTS-13 cleavage of ultra-large von Willebrand factor (UvWF)

Ectonucleotidase expression

Release of nitric oxide (NO)

Prostacyclin production

Waterfall Cascade Interactions

Tissue factor pathway inhibitor (TFPI) release

Endothelial protein C receptor expression

Protein C activation via expression of thrombomodulin

Anti-thrombin III binding

Gas6 production and release

Fibrinolysis

Tissue plasminogen activator (tPA) production

Urokinase type-Plasminogen Activator Receptor (UPAR) expression

Plasminogen Activator Inhibitor-1 (PAI-1) induction

List 2

Interactions between coagulation and inflammation

Coagulation and inflammation are inextricably linked biologic defense mechanisms. Multiple interrelated processes exist that aid in defense and healing. Extreme activation of these processes may also be considered maladaptive at times, as is the case with activated protein-C related trauma induced coagulopathy (TIC). PAR-1=protease activated receptor-1, uPA=urokinase-type plasminogen activator, uPAR=uPA receptor.

<u>Anti-inflammatory roles of anticoagulants</u>	<u>Inflammatory activation of coagulation</u>
Antithrombin: <ul style="list-style-type: none"> • Via induction of endothelial prostacyclin release <ul style="list-style-type: none"> – blocks neutrophil/endothelial tethering – decreases endothelial cytokine production • Blocks neutrophil, monocyte, and lymphocyte endothelial interactions • P-selectin down-regulation Protein C: • Via PAR-1, blocks nuclear factor-κB translocation • Vascular permeability barrier preservation • Down-regulates inflammatory response Protein S: • Facilitates apoptotic cell phagocytosis • Down-regulates intracellular inflammatory pathways via acting as a ligand for innate immune cell tyrosyl-, axyl-, mer-(TAM) receptors 	Cytokines induce tissue factor expression Inflammation down regulates the Protein-C system Inflammation inhibits fibrinolysis Inflammatory platelet activation
	<u>Coagulation activation of inflammation</u> Platelet activation of monocytes uPA/uPAR macrophage activation Fibrin, thrombin, FXa, & FXa complexes activate monocytes, macrophages, mast cells & endothelium

List 3

Contributors to Trauma Induced Coagulopathy (TIC)

TIC, an acute coagulopathy seen immediately after severe trauma, is a multifactorial disorder.

TIC Contributors

Severe tissue injury

Shock induced tissue hypoperfusion

Excessive and prolonged inflammatory response

Systemic endothelial degradation

- Auto-heparinization
- Weible-Palade body degranulation and tPA associated hyperfibrinolysis

Platelet dysfunction

Maladaptive protein C response

Fibrinogen depletion

List 4**Damage control resuscitation**

Trauma resuscitation must be goal directed and prompt in order to attain the best potential outcome. These goals are listed.

Goals of Trauma Resuscitation addressed by Damage Control Resuscitation

- Identify patients at risk for “massive transfusion”
 - Prompt initiation of appropriate hemostatic resuscitation
 - Prevent bleeding induced by excessive blood pressure
 - Improve tissue perfusion
 - Minimize crystalloid resuscitation
 - Minimize hemodilution of factors
 - Treat/prevent hypothermia
 - Correct acidemia
-

List 5

Modified Society of Thoracic Surgeons recommendations

The 2011 Society of Thoracic Surgeons blood conservation guidelines have been condensed and modified for broader application.

-
- **Creation of multidisciplinary blood management teams is considered important in prevention and treatment of massive bleeding.**
 - **Identification of patients at high risk of requiring blood transfusions**
 - Advanced age
 - Low preoperative red cell volume
 - Antiplatelet/antithrombotic drugs preoperatively
 - Complex procedures
 - Emergency operations
 - Comorbidities
 - **Preoperative risk reduction strategies**
 - Correction of anemia before surgery
 - Use of antifibrinolytic drugs
 - Selective use of alternative procedures with lower bleeding risk
 - Appropriate modification of antiplatelet/anticoagulant therapy
 - Discontinuation/bridging based upon most recent guidelines
 - Prothrombin complex concentrates (PCC) reversal of warfarin for emergency surgery
 - Platelet function testing for those on antiplatelet therapies
 - **Intraoperative**
 - Cell salvage
 - Factor replacement when rapid POC testing shows specific source(s)
 - Fractionated products if available
 - Plasma acceptable when safer fractionated products are unavailable
 - Factor replacement when rapid POC testing unavailable
 - Plasma acceptable when used as part of a MT algorithm
 - Topical hemostatic agents
 - Compression devices
 - Sealants after cell salvage
 - Antifibrinolytics poured into the wound after cell salvage
 - **Postoperatively**
 - Continued monitoring of bleeding and coagulation status
 - Treatment as indicated
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