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THOR Position Paper on Remote Damage Control Resuscitation: Definitions, Current Practice and Knowledge Gaps

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Keywords

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The Trauma Hemostasis and Oxygenation Research (THOR) Network held its third annual Remote Damage Control Resuscitation (RDCR) Symposium in June of 2013 at Solstrand Hotel, near Bergen Norway. THOR is a multidisciplinary group of clinical, translational and basic investigators with a common interest in improving outcomes and safety in patients with severe traumatic injury. The Network's mission is to reduce the morbidity and mortality from traumatic hemorrhagic shock, in the pre-hospital phase of resuscitation through education, training and research.

RDCR has been defined as the pre-hospital application of Damage Control Resuscitation (DCR) concepts (1, 2). DCR principles include: compressible hemorrhage control; hypotensive resuscitation; rapid surgical control of bleeding; avoidance of the overuse of crystalloids and colloids, prevention or correction of acidosis, hypothermia, and hypocalcemia; and hemostatic resuscitation (early use of a balanced amount of red blood cells (RBCs), plasma, and platelets).(3) The term RDCR was first published by Gerhardt and colleagues from the United States Army Institute of Surgical Research and since been promoted by the THOR Network.(1, 2, 4) The initial definition of DCR, by Holcomb and colleagues, states "DCR addresses the entire lethal triad immediately upon admission to a combat hospital".(3) Others have promoted expanding the definition to include care from the point of injury.(5) Since early identification and treatment of hemorrhagic shock may improve outcomes, we contend that the distinction between RDCR and DCR is an important one since there are differences in capabilities, and in some cases optimal management strategies between pre-hospital and in-hospital care. These differences may include availability of blood products and monitoring capabilities, as well as the lack of evidence to

support the use of hypotensive resuscitation strategies for delayed or prolonged evacuation and the associated risks with airway management for casualties in hemorrhagic shock.

The debate over the appropriate term for pre-hospital resuscitation concepts and others discussed at the RDCR Symposium's in the past has motivated the leadership to produce a position paper. The aim of this paper is to offer standardized definitions of key components of RDCR by which one could truly compare techniques, strategies, products/devices and outcomes; define the currently acceptable ranges of practice (from soldiers to medics to physicians); and identify knowledge gaps in RDCR that should be addressed with future research.

Shock and Oxygen Debt

Shock is defined as a pathophysiological state that occurs when oxygen delivery is insufficient to maintain aerobic respiration in tissue. Reduced perfusion often accompanies shock but is not essential for its development. The consequence of persistent shock is cell death due to inadequate energy production. An oxygen deficit is incurred when oxygen delivery falls below levels necessary to support aerobic metabolism.(6) In this context, *oxygen debt* can be understood as the ongoing quantifier of the degree of shock and has been correlated with not only death but complications of shock such as inflammation, acidosis, coagulopathy, and multiple organ failure.(7–11) It is not enough to simply halt the accumulation of oxygen debt: it must be repaid. The timing and degree to which oxygen debt is repaid is key to survival and mitigation of organ failure.(6, 8, 9, 11)

Hemostasis and Coagulopathy

Our understanding of hemostasis has been advanced substantially with the cell-based model proposed by Roberts et al.(12, 13) *Hemostasis* is a physiological process, which in the context of traumatic injury, is initiated when tissue damage exposes tissue factor, which activates coagulation factors to produce thrombin and fibrin. Platelets catalyze thrombin generation by amplifying a thrombin burst once they are activated in the presence of thrombin. Platelets also form the initial platelet plugs at points of vascular injury, activate immune effector cells, secrete growth factors, and exert mechanical tension on clot structure, which, together with sympathetic nerve activity and adrenergic neurohormonal signaling, causes vasoconstriction. Red cells contribute to clot formation by adding bulk and by causing platelet margination to the vascular wall in flowing blood, facilitating platelet plug formation. Hemostasis is tightly regulated by multiple biochemical processes including endothelial suppression of platelet activation through nitric oxide (NO) and prostacyclin secretion, activation of anticoagulant enzymes such as the Protein C and S pathways, and fibrinolytic systems involving plasminogen activators and plasmin.(14, 15) Furthermore, hemostatic activity may be limited, in the short term, by the availability of substrate, namely fibrinogen, von Willebrand factor, and platelets.(16, 17) The activity of this system is also modulated by pH, temperature and the hemodilution that occurs from crystalloid resuscitation and reversal of Starling forces with shifts of fluid from the interstitium to the vascular compartment during hemorrhage.(18–20) A *thrombus* is the final result of the hemostatic process of clot formation. Conversely, thrombosis, is the result of a

pathophysiologic process of inappropriate intravascular clotting, which causes tissue injury. (21)

Coagulopathy secondary to trauma encompasses abnormalities in clot formation due to a continuum of elaborate hemostatic and immunoinflammatory responses to injury that can result in a pathophysiological state where the net effect is either a predominantly hypocoagulable or hypercoagulable state. *Hypocoagulability* is a pathophysiological process that leads to a reduction in hemostatic potential that increases the risk of bleeding. *Hypercoagulability*, also a pathophysiological process, leads to a pro-thrombotic environment. In complex pathophysiological conditions, due to severe traumatic injury and resuscitation, both hypo and hypercoagulable tendencies can exist simultaneously, due to local conditions across vascular beds. In addition, in critically ill patients with severe traumatic injury, hemostatic potential often changes over time from hyper to hypocoagulable or hypo to hypercoagulable. For example, it has been observed that activation of Protein C occurs in severely injured patients, and that this correlates with depletion of factors V and VIII. The net result of these and other changes, such as depletion of fibrinogen and hemodilution, results in hypocoagulable state. However, activation of protein C requires generation of sufficient thrombin to allow interaction with thrombomodulin suggesting a prior hypercoagulable state not appreciated by laboratory investigation at the time of patient admission to hospital. Multiple factors such as severity of tissue injury, injury location, degree of shock, inflammatory and endothelial response, genetic influences, and resuscitative or iatrogenic factors can influence hemostatic potential.

The complexity of these biological relationships is reflected in the nomenclature assigned over the past half-century to observations of apparently abnormal coagulation associated with trauma and resuscitation: Disseminated Intravascular Coagulation (DIC), Acute Coagulopathy of Trauma and Shock, Acute Traumatic Coagulopathy (ATC), and Trauma-induced Coagulopathy (TIC).

ATC characterized by increased activated protein C and fibrinolysis was proposed to distinguish the primary or endogenous coagulopathy that occurs as a result of severe traumatic injury from subsequent secondary or exogenous alterations such as iatrogenic factors during resuscitation.(22, 23) The appreciation of this phenomenon has been very important in describing an unknown pathway underlying a direct mechanism for coagulopathy after severe traumatic injury. These endogenous mechanisms go beyond Protein C and fibrinolysis and also include additional mechanisms such as catecholamine release and pro-inflammatory signaling, in addition to many other unknown pathways. TIC is a broader term that has been used to describe both endogenous (primary) and exogenous (secondary) causes of coagulopathy following trauma. While it is useful to have a term that encompasses all potential mechanisms of trauma-related coagulopathy, it is less helpful as a term when the goal is to discuss specific mechanisms. Neither of these terms, as currently defined, are optimal. As a result they are often misapplied or used incorrectly in the literature. In fact, just obtaining consensus regarding the meaning of these terms amongst leaders in this field within the THOR Network was elusive.

Consensus may be more achievable if researchers in this field agree to recognize a simple division between the acute, primary (endogenous) coagulopathy, and secondary (exogenous or iatrogenic) coagulopathies. We propose that the *Primary Coagulopathy of Trauma* include all mechanisms that occur as a result of biologic response to traumatic injury and that the *Secondary Coagulopathy of Trauma* includes all exogenous or iatrogenic causes of coagulopathy. The characterization of this secondary coagulopathy will be difficult since resuscitation practices vary significantly and have evolved considerably in recent years.

Endotheliopathy of Trauma

The endothelium is the platform on which a number of biological processes take place in both health and disease.(24, 25) Over the past few years the systemic impact of hemorrhagic shock on the endothelium has become more widely recognized.(25–27) Aside from direct trauma to the vasculature, severe hemorrhage is associated with decreased organ perfusion, vasoregulatory changes and ischemia-reperfusion injury to both the endothelium and surrounding tissue. The term “endotheliopathy of trauma” (EoT) has been used to globally describe the consequences of this systemic endothelial injury caused by trauma and hemorrhage leading to disturbances in the tightly regulated processes of: 1) coagulation; 2) inflammation; 3) blood-organ endothelial barrier integrity; and 4) vasoregulation. Pathologically these processes are associated with vascular leak, tissue edema, microvascular thrombi, diminished organ perfusion, uncontrolled hemorrhage and organ injury.

Although there are not clear parameters of endothelial dysfunction that can be used to characterize and quantify EoT, a few possible candidates include disruption of the endothelial glycocalyx, reactive oxygen species production, deregulated production of NO, protease (sheddase) activation, transcellular and paracellular permeability, vascular endothelial junctional stability, inflammatory markers, and vasoreactivity. Examples of serum biomarkers for vascular endothelial dysfunction include circulating histone complexed DNA fragments, vWF, syndecans (surrogates for injury to the glycocalyx), s-P-Selectin, s-E-Selectin, s-ICAM-1, s-VCAM-1, tissue factor, endothelin-1, homocysteine, eNOS, PAI-1, Superoxide dismutase, and tPA.(27, 28)

We hypothesize that the EoT can be used as a therapeutic target for the development of novel drugs, therapies and resuscitation paradigms to improve clinical outcomes in trauma. Pre-clinical work by a number of groups has demonstrated that fresh frozen plasma (FFP) has the capacity to ameliorate vascular endothelial permeability and inflammation caused by traumatic injury. (25–27, 29) Clinical studies with DCR suggest that increased use of FFP improves outcomes after trauma and hemorrhage.(30) The clinical consequences of decreased vascular permeability and inflammation on trauma related outcomes have yet to be determined. This definition of EoT is an attempt to capture its characteristics, etiology, and possible measurement. As the mechanisms responsible for the EoT are largely unknown, this definition is likely incomplete but provides the foundation for future investigations.

Life Saving Intervention and Evacuation Location and Duration Definitions

A *lifesaving intervention* is defined as a medical procedure that if not performed conveys a high probability of increased morbidity or death. The terms *remote* and *forward* both are to be defined as the pre-hospital setting or phase of resuscitation. The terms *far-forward* and *austere* are defined as the environment where professional health care providers normally do not operate and basic equipment and capabilities necessary for resuscitation are often not available. Typically the austere environment poses challenges like limited access to power supply, sheltered treatment facilities, exposure to different light conditions, weather, altitude and ongoing threat from the enemy in military scenarios. To describe the duration of evacuation times, the term *delayed* evacuation will be defined as >60 minutes from wounding until reaching a medical treatment facility (MTF) that is capable of providing Damage Control Surgery (DCS) and DCR. The term *prolonged* evacuation will be defined as >6 hours from point of wounding until arrival at an MTF capable of providing DCS. These definitions apply equally to both civilian and military environments. While they could be considered somewhat arbitrary, they are commonly used definitions with evidence to support their use in literature. (31)

Hemostatic Adjuncts

Hemostatic adjuncts are either mechanical or injectable. Both have advantages in different scenarios and can ideally be combined to best affect hemorrhage control.

Mechanical hemostatic adjuncts include; extremity tourniquets, junctional tourniquets, abdominal tourniquets and gauzes impregnated with pro-coagulants. More invasive types of mechanical devices to stop bleeding have recently gained increased interest. Resuscitative Endovascular Balloon Occlusion of the Aorta is an example of an emerging technique that might be considered for use in the prehospital environment.(32) *Injectable hemostatic adjuncts* include manufactured/derived hemostatic agents like plasma derivatives such as solvent detergent treated plasma or lyophilized plasma products, fibrinogen, prothrombin complex concentrates (PCC), Recombinant human Factor VIIa (rFVIIa), other factor concentrates, calcium, magnesium, and tranexamic acid (TXA).

Labile Blood Products and Biologics derived from Plasma

Several therapeutic products are derived from human blood, which in most countries, are divided into two *primary categories: 1) Labile blood products and; 2) biological medications* derived from plasma by fractionation and concentration techniques.

Labile blood products are obtained by separation of whole blood into plasma, red blood cells, platelets and leukocytes and are intended for transfusion therapy. Whole blood is further categorized according to the temperature and duration of its storage. The term *Warm Whole Blood* (WWB) is used when the blood is maintained at 22–26 Celsius after donation. If the donated blood is cooled to 2–6°C, it is referred to as *Cold Whole Blood* (CWB). Whole blood stored for less than 48h is referred to as “fresh”. All other blood products, such as platelets, plasma or packed red cells, are referred to as *blood components*. These products are not regulated as pharmaceuticals (they do not undergo a licensing process that includes

precise manufacturing, biochemical, pharmacokinetic, safety and efficacy characterization that is reflected in a drug package insert). However, they are subject to strict export restrictions traceability and hemovigilance requirements (i.e. the notification of adverse events and transfusion reactions).

Biological medications extracted from plasma by protein fractionation and concentration techniques, such as the previously mentioned hemostatic adjuncts, are regulated as pharmaceuticals (biologics); undergo a rigorous licensing process that includes precise product characterization and regulation of manufacturing and quality control; and are subject to pharmacovigilance requirements.

Endpoints of Resuscitation

Re-establishing adequate end-organ perfusion, restoring normal coagulation and re-paying oxygen debt are the essential *endpoints of resuscitation*. Rudimentary assessment of the endpoints of resuscitation applicable in RDCR is found in guidelines currently recommended in a number of formats globally, namely the US Tactical Combat Casualty Care Guidelines and UK Battlefield Advanced Trauma Life Support.(33) Field expedient observations, such as restoration of palpable radial pulse or improvement in level of consciousness are endorsed as adequate endpoints of fluid resuscitation, although little data is available to support their use. No attempt is made to establish adequacy of tissue perfusion using any sort of device or laboratory test due to the remoteness and/or austerity of the environment.

Level 1 evidence suggests standard hemodynamic parameters do not adequately quantify the degree of physiologic derangement in trauma patients. Lactate level and initial base deficit can be used to identify the need for ongoing fluid resuscitation and the risk of organ dysfunction and death. Level 2 evidence reveals the time to normalization of base deficit and lactate is predictive of survival and that monitoring of at least one of these parameters should be used for prognostication and that a persistently elevated base deficit or lactate (or worsening of these parameters) may be an early indicator of inadequate resuscitation and should prompt rapid reassessment of the patient. Finally, Level 3 evidence demonstrates that parameters not currently available in RDCR scenarios such as right ventricular end diastolic volume index measurement may be a better indicator of adequate volume resuscitation (preload) than central venous pressure or pulmonary capillary wedge pressure. Also, measurements of tissue (subcutaneous or muscle) O2 and/or CO2 levels may be used to identify patients who require additional resuscitation and are at an increased risk for organ failure and death.

CURRENT RANGE OF PRACTICE

Pre-hospital use of blood components and products: Dried Products

While it is generally accepted that blood (usually in the form of component therapy) should be used for resuscitation of bleeding patients in shock, technical, regulatory and logistical limitations may prohibit the use of blood components in the pre-hospital setting.(34) Packed red blood cells require refrigeration, FFP requires freezing and a time-consuming thawing

process, platelets are stored at 22°C on special agitators and cryoprecipitate is also frozen, thus making the performance of RDCR with hemostatic resuscitation practically impossible, under most circumstances. Dried blood products, (freeze or spray dried), stored at room temperatures for extended periods of time, offer the potential for blood products to be administered in the pre-hospital environment. Attempts to produce the “holy grail” of freeze dried whole blood, in the form of a unit of autologous whole blood, pre-collected, dried and carried by each soldier or first responder (to allow volume and oxygen carrying capacity resuscitation) continue, but it is far from being commercially available.(35)

As of now, freeze dried plasma (FDP) is the only field-ready freeze dried whole plasma product that offers freedom from some of the logistical constraints involving the use of blood products in the pre-hospital and remote settings. Currently, plasma is available for casualty care in Afghanistan at the Role 2 and 3 fixed hospitals (German and French), and FDP is carried by providers in a few special operation units. The Israeli Defense Forces uses FDP(36) across all services, at the point of injury and the Norwegian Air Ambulance system also uses FDP in the pre-hospital setting for RDCR.

Use of whole blood

Based on the current literature our position is that whole blood should be used for life saving emergency transfusions if there are no acceptable alternatives. If ABO type specific whole blood is not available, or if it is not feasible to accurately determine the ABO type of the donor and recipient, low titer Type O whole blood is ideal.(37) However it is impossible to perform the hemolysin antibody titration in the field, so this titer should be known in advance. The titer is defined as the reciprocal value of the highest dilution of a serum but a well-accepted definition of “low titer” has not been established internationally. For example, the Swedish military uses the “low titer” for the A or B antibodies below 100 for IgM and 400 for IgG. For non-emergency situations ABO-compatible blood products should be used whenever possible. In a situation where it is not possible to determine the ABO Type of the donor or recipient, and it is not known if a potential Type O donor is “low titer”, then the Type O donor should be used as a last resort for patients with life-threatening hemorrhagic shock if the benefits of providing the whole blood is perceived to be higher than the risk of a severe hemolytic reaction. (37)

There is considerable experience using whole blood, particularly from the transfusion of “hemolysin low titer” group O blood units in military service, showing that the frequency of severe hemolytic reactions due to the transfusion of anti-A and anti-B antibodies is negligible for these transfusions. Platelet units contain a clinically significant amount of plasma. The wide spread use of group O platelet units containing incompatible ABO-antibodies has resulted in a small number of reports of intravascular hemolytic transfusion reactions. However, these reactions are mainly seen in the use of platelets in patients with a systemic malignancy or in children and there are few with a fatal outcome. (38)

Transfusion Transmitted Disease Testing or Screening of Donors

Because blood transfusion is a central element in the concept of RDCR it would be preferable to have a supply of fully tested blood products on hand to reduce the risk of

Transfusion Transmitted Diseases (TTD), but this may not be possible due to logistical constraints.

Current options for maximizing blood safety include the use of pre-tested donors and rapid testing at the time of donation. The following steps to minimize whole blood TTD risks should be considered.(37) Prior to deployment, all personnel should undergo immunization against Hepatitis B Virus (HBV), and if possible screening for HIV. Volunteer blood donors should be screened and fully tested for TTDs at a minimum in compliance with World Health Organization (WHO) standards Blood samples should be sent to laboratories for nucleic acid testing for Human immunodeficiency virus (HIV), HBV surface antigen (HBsAg), Hepatitis C virus (HCV), and syphilis. Testing may be enhanced to conform to national standards and may include additional testing such as the use of nucleic acid testing and West Nile Virus (WNV), malaria, dengue and Chagas disease. Donor testing, while logistically challenging, should be repeated at pre-agreed upon intervals such as every 90–180 days.(39)

Pre-testing for members of small units operating in austere environments can maximize number of donors for buddy transfusions. Rapid tests exist for HIV, HBsAg, HCV, syphilis (RPR), and malaria.(40) Not all of these rapid tests have been approved by all regulatory bodies. Finally, where no samples have been taken at the time of donation, both donors and recipients should be retrospectively tested by sending blood samples to reference labs.

TTD risk in far-forward transfusion of whole blood during RDCR currently depends on the prevalence of disease in the specific donor population, force protection measures including immunization, insect repellant use and anti-malarial prophylaxis, the frequency and accuracy of donor testing, record keeping, and the use of rapid tests. More convenient rapid tests are under development as well as pathogen reduction technologies (PRT) that could be used in field blood banks.(41, 42) Refrigeration of CWB after pathogen reduction could ensure wide availability, hemostatic efficacy and enhanced safety in far forward settings, but must be weighed against its logistic burden.(43)

Hypotensive Resuscitation in Delayed/Prolonged Evacuations

Hypotensive resuscitation is based on the assumption that in patients with noncompressible hemorrhage, raising blood pressure above a critical value may result in increasing hemorrhage including “popping” of naturally formed clots at the site of injury. While this approach has now evolved into a current combat casualty care doctrine for the combat medic by inferring adequate perfusion through pulse quality and mental status, all clinical data supporting its use come from studies where time from injury to definitive surgical care is very short, where higher ratios of medical personal to wounded are present and monitoring options are more robust.(33, 44–47) The degree to which hypotensive resuscitation can be utilized in a prolonged or delayed evacuation is unknown.(48) The risk of prolonged hypoperfusion and shock and resultant coagulopathy may cause substantial cellular injury. While the use of hypotensive resuscitation in prolonged or delayed evacuations should be used with caution due to the lack of evidence supporting this strategy, patients should never be over-resuscitated to the point where they are hypertensive regardless of the evacuation time.

Injectable Hemostatic Adjuncts

The logistical challenges of resuscitating trauma patients in remote settings often limit or preclude administration of blood products. Bleeding patients may benefit from treatments that support hemostasis, particularly when intravascular volume is supported with crystalloid fluids, which may result in dilutional coagulopathy. Improvement of clot stability: The CRASH-2 trial demonstrated that the anti-fibrinolytic TXA , administered upon admission to hospital within 3 hours of injury, reduced all-cause mortality and death due to hemorrhage in trauma patients without an increase in venous thromboembolism (VTE).(49, 50) Similar findings were reported in the MATTERs2 study of combat casualties in Afghanistan although a higher rate of VTE was identified (unadjusted data) in those receiving TXA which may be a result of surviving the initial injury. (51) Given that earlier administration of TXA resulted in improved outcomes in CRASH-2, use in the pre-hospital setting appears to be a reasonable extrapolation of the available clinical data. Furthermore, TXA is stable across a wide range of environmental conditions.(52, 53) To that end THOR endorses the **North Atlantic Treaty Organization** (NATO) approach to the use of TXA as part of a protocol for the resuscitation of patients in hemorrhagic shock.

Improvement of clot quality: Fibrinogen is the ultimate substrate of the coagulation system and is vulnerable to rapid depletion in the setting of massive trauma and hemorrhage due to hemodilution, consumption and fibrino(geno)lysis.(54–56) Fibrinogen concentrates appear to be safe even when given in high doses, and may rapidly restore hemostatic function, thus reducing bleeding and blood product requirements.(57, 58) In one large population study of severely injured patients, the early use of fibrinogen concentrate was associated with significantly lower 6-hour mortality and an increased time to death, but also an increased rate of multiple organ failure. (59) Randomized trials, particularly in the pre-hospital setting, are urgently needed to guide appropriate use of this promising agent in trauma resuscitation.

Improvement of thrombin generation: rFVIIa has been evaluated as a hemostatic adjunct in trauma and in other bleeding patients. While rFVIIa likely reduces bleeding and red cell transfusion requirements, no mortality benefit has been attributed to use of this drug and it increases thromboembolic risk in certain patient populations (e.g., elderly, active atherosclerotic vascular disease).(60, 61) Its use in trauma as a hemostatic adjunct cannot be recommended outside of a clinical trial setting.

PCCs have become the new standard of care in managing hemorrhage in the setting of warfarin anticoagulation.(62) Their use in a broader population of trauma patients has not been evaluated adequately in randomized controlled trials (RCT’s). Animal studies suggest that PCCs may be useful in reducing blood loss but may also increase the risk of developing DIC.(63, 64) Further controlled clinical studies are required before the use of PCCs can be recommended for the broader trauma population.

Mechanical Hemostatic Adjuncts

Direct compression with gauze is an age-old standard by which all other methods are measured. Gauze/bandages impregnated with substances with additional hemostatic properties (zeolite, kaolin, chitosan, etc.) are commercially available, durable, and generally

of substantial benefit over traditional gauze and are routinely employed in RDCR scenarios. Training is minimal and risk to the casualty is also minimal. Extremity tourniquets have seen resurgence in use and have proven beneficial.(65) More recently, junctional tourniquets have been employed with specific direction for training and use, but evidence of their effectiveness in RDCR has yet to be established.(66) Control of 'non-compressible' hemorrhage in the torso, is the next step in RDCR; devices are under development to occlude blood vessels by percutaneous insertion of balloon occluding catheters(32) and substances are being developed which can be injected percutaneously through wounds into the abdominal cavity, which will expand and provide temporary hemorrhage control. No recommendation can be made as to their role in hemorrhage control in the remote environment.

KNOWLEDGE GAPS WHERE FUTURE RESEARCH ENDEAVORS ARE NEEDED

Pre-Hospital Monitoring Of Shock and Coagulopathy

Pre-hospital monitoring in trauma resuscitation is commonly based on clinical experience and a few basic parameters (i.e. consciousness, blood pressure, heart rate, respiratory rate, capillary filling time, and capnometry).(67, 68) But even if these are normal or close to normal, shock at the cellular or organ level may still be present.(69, 70) Options for real-time physiological assessment and optimum hemodynamic monitoring including coagulation during pre-hospital resuscitation are limited by logistics, cost and training. Advanced Point-of-Care (PoC) devices may substantially support serial and repeated measurements of arterial blood gases, lactate and hemoglobin to provide important information to the caregiver. Future options may include PoC ultrasound, hemostasis and biochemical monitoring and continuous tissue oxygen saturation.

Hypotensive Resuscitation

The duration of a hypotensive resuscitation strategy, proper patient selection and monitoring for adverse effects of its use are necessary. This is an important area of research that requires prioritization since a large proportion of patient evacuations are greater than one hour.

Endpoints for Resuscitation

While hospital based end points are dependent upon monitoring devices and blood tests that are impractical in the austere setting today, there has been little attempt to make such technology available in the far forward arena. As is currently utilized by both the London Helicopter Emergency Medical Service and Norwegian Air Ambulance systems, can ultrasound of the vena cava diameter or estimation of stroke volume or tissue oxygen delivery be measured effectively with appropriate training in a RDCR environment? Is there a combination of these parameters that can best define that resuscitation has been successful or needs to continue? In the setting of hypotensive resuscitation, are the parameters for setting endpoints substantially different in RDCR? What triggers for cessation of transfusion would be best utilized? What would be the appropriate interval between administration of blood products and/or other hemostatic substances in order to maintain perfusion without

"popping the clot" if evacuation is prolonged? What are the morbidity and mortality, if any, associated with hypotensive resuscitation in the setting of mild to moderate traumatic brain injury (TBI)? Are there other substances that can protect cells from the effects of shock and improve outcome if administered pre-mission/pre-injury. Is resolution of coagulopathy and end point in itself or merely another parameter that is a critical factor to the overall resuscitation? Again, many questions need to be answered before evidence-based guidelines can be developed to determine appropriate endpoints of prehospital shock resuscitation.

Whole blood compared to blood components for hemostatic resuscitation

Currently there are no high quality data comparing the effectiveness or safety of a whole blood based versus a blood component based hemostatic resuscitation approach for patients with traumatic injury. An adult trauma study was just published that compared the use of modified whole blood plus apheresis platelet units to the use of only blood components. This trial did not show a difference in blood product use with either therapy.(71) Unfortunately, since this study did not exclusively compare whole blood to blood components it does not provide direct data to determine if the exclusive use of whole blood is more efficacious compared to blood components. Other aspects that make the trial not generalizable are that the whole blood was leukocyte reduced with a filter that removes platelets. Current technology allows for platelet sparing leukocyte filters that are in clinical use in civilian and military settings.

Retrospective adult trauma studies and pediatric RCTs analyzing the efficacy of warm and cold whole blood in patients requiring cardiac surgery have demonstrated mixed results.(72–77) With the resurgence of interest in the hemostatic effect of platelet containing products stored at 2–6°C, there is also renewed interest in performing trials comparing CWB, stored at 2–6°C for up to 10 days, compared to reconstituted whole blood from blood components. These trials are very important to perform since there are no high quality data in the literature to determine which approach will optimize outcomes and safety in patients with traumatic injury. These trials should also include patients identified with life-threatening hemorrhagic shock in the prehospital setting.

The current practice of storing platelets at room temperature with constant agitation for a maximum of 5 days results in increased risk of bacterial contamination, constrained inventories and decreased hemostatic function compared to storage under refrigeration, the standard of care until the 1980s.(43, 78–80) The need for a practical way to provide hemostatically functional platelets to support RDCR suggests that platelet and whole blood refrigeration should be re-examined. The current standard of platelet storage, and by extension, limitation on whole blood use, is impractical for RDCR. Clinical outcomes for patients with hemorrhagic shock could potentially be improved by studies of refrigerated or frozen platelets or warm or cold whole blood.

Dried product efficacy and safety

Knowledge gaps regarding the use of freeze dried blood products (only plasma has been currently developed with this technology) remain, despite its extensive use in previous wars.(81) There are several fundamental questions that need to be answered. Are lyophylized

plasma products equally efficacious to standard plasma? Are there increased risks with its use? Are pooled products more or less efficacious/safe than single donor products? Does spray drying vs. freeze drying effect efficacy or safety? Many other challenges await us, such as determining the efficacy and safety of mixing different freeze dried blood products (in an attempt to "re-constitute whole blood"), in addition to the effect on combining lyophylized blood products with TXA or other injectable hemostatic agents.

Pathogen Reduced Technology for Blood Products

Over the past few decades multiple PRT processing methods for blood products have been licensed for plasma and platelet products.(82–85) Processing methods for plasma include: amotosalen; solvent detergent treatment; nanofiltration; methylene blue and; ultra violet (UV) light with riboflavin. PRT for platelets include psoralens and UV light with riboflavin. No methods are licensed for RBCs or whole blood, but PRT for RBCs using psoralens and UV light with riboflavin for RBCS and whole blood are in development.

These PRT products not only have the benefit of reducing the risk of TTDs, but based upon their processing methods may offer additional benefits including: 1) reducing microparticle and WBC loads that appear to promote immunomodulation and a pro-thrombotic state, 2) pooling of plasma donors which appears to reduce the risk of transfusion related acute lung injury, and 3) pooling of plasma donors which produces a consistent product regarding coagulation factors compared to single donor plasma products that have wide variation in all proteins in plasma.

Research is needed to determine if PRT treated products provide significant improvement in outcomes for patients with severe traumatic injury. It is unknown if the increased safety of these products is at the expense of reduced efficacy. It is also unknown if the increased cost of these products is worth the potential clinical benefits as well.

The Role of Traumatic Brain Injury in the Approach to Resuscitation

The complex pathophysiological mechanisms of the coagulopathy of TBI is poorly understood, but includes a combination of both hypo- and hypercoagulable states promoted by the magnitude of the brain tissue injured. (86) The underlying mechanisms may comprise the release of tissue factor, hyperfibrinolysis, shock and hypoperfusion thus triggering the protein C pathway, disseminated intravascular coagulation, and platelet dysfunction.(87) Further research is needed to determine the most effective methods to determine optimal methods to monitor and treat shock and coagulopathy for patients with severe TBI.

Prospective Observational Data Collection

High quality prospective observational data collection into registries plays a critical role in trauma research and quality improvement. Currently there is no multicenter registry of patients resuscitated with blood products or hemostatic agents in the prehospital setting. As RDCR is rarely practiced today and not well documented, establishing a prehospital registry that incorporates the use of blood products and hemostatic agents in sufficient detail would offer many benefits to the study of RDCR and should be a trauma research priority. Where

robust registries already exist, adding fields to specifically address the RDCR elements would be practical. Where that is not possible, a registry could be developed and used to:

1. Examine the feasibility of prehospital transfusion and hemostatic use.
2. Highlight what potential patient populations may benefit most from specific interventions.
3. Suggest what prehospital strategies may hold most benefit.
4. Provide large dataset to answers questions regarding unique types of situations or patients.
5. Provide support for investigator-initiated study.
6. Inform future clinical trials of prehospital hemostatic use.
7. Provide data to support applications for extramural funding to support clinical trials.

Collection of high-quality prehospital data can be plagued by problems with data standardization, chaotic prehospital environments, limited personnel, and multiple hand-offs. However, these challenges can be overcome by a well-planned and well-coordinated effort among registry providers so that valuable insights into remote resuscitation can be made.

Optimal Clinical Trial Design For RDCR Therapies

Studies in the RDCR setting are methodologically challenging. Some methodological approaches may be helpful in performing studies in the RDCR setting, such as: 1) Cluster randomization (based upon units, wards or regions rather than by individual patients) eliminates delay caused by the need to randomize a presenting patient, and reduces the number of patients missed for inclusion. Although the randomization occurs at group level, if set up and performed correctly, individual patient outcomes may still be analyzed.(88); 2) sequential analyses: with every endpoint reached, an analysis is performed to check whether the study should continue (answer still unknown) or be stopped (answer known or continuation futile). This approach may vastly reduce the number of inclusions, but the exact study size cannot be determined beforehand. (89, 90)

Conclusion

The concept of RDCR is in its infancy and there is a significant amount of work that needs to be done to improve outcomes for patients with life-threatening bleeding secondary to injury. The pre-hospital phase of their resuscitation is critical and if shock and coagulopathy can be rapidly identified and corrected prior to hospital admission this will likely reduce morbidity and mortality. The THOR Network is committed to improving outcomes for patients with traumatic injury through education, training and research. This position statement begins to standardize the terms used, provides an acceptable range of therapeutic options, and identifies the major knowledge gaps in the field.

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ABBREVIATIONS

ATC	Acute Traumatic Coagulopathy
CWB	Cold Whole Blood
C	Celcius
CO2	carbon dioxide
DCR	Damage Control Resuscitation
DCS	Damage Control Surgery
DIC	Disseminated Intravascular Coagulation
DNA	Deoxyribonucleic acid
eNOS	endothelial nitric oxide synthase
EoT	Endotheliopathy of Trauma
FDP	freeze dried plasma
FFP	fresh frozen plasma
HBSG	Hepatitis B Virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C virus

HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IgM	Immunoglobulin M
MTF	medical treatment facility
NATO	North Atlantic Treaty Organization
NO	Nitric Oxide
O2	Oxygen
PAI-1	Plasminogen activator inhibitor-1
PCCs	prothrombin complex concentrates
PoC	Point-of-Care
PRT	Pathogen Reduction Technique
RBCs	red blood cells
RCTs	randomized controlled trials
RDCR	Remote Damage Control Resuscitation
rFVIIa	Recombinant human Factor VIIa
RPR	rapid plasma reagin; s-E-Selectin; s-P-Selectin; s-ICAM-1 s-VCAM-1
TBI	Traumatic Brain Injury
THOR	Trauma Hemostasis and Oxygenation Research
TIC	Trauma-induced Coagulopathy
tPA	Tissue plasminogen activator
TTD	Transfusion Transmitted Disease
TXA	tranexamic acid
UV	ultra violet
VTE	venous thromboembolism
vWF	Von Willebrand factor
WHO	World Health Organization
WNV	West Nile Virus
WWB	Warm Whole Blood

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