SHOCK, Vol. 41, Supplement 1, pp. 3–12, 2014

TRAUMA HEMOSTASIS AND OXYGENATION RESEARCH POSITION PAPER ON REMOTE DAMAGE CONTROL RESUSCITATION: DEFINITIONS, CURRENT PRACTICE, AND KNOWLEDGE GAPS

Donald H. Jenkins,* Joseph F. Rappold,† John F. Badloe,‡ Olle Berséus,§ COL Lorne Blackbourne,‖ Karim H. Brohi,¶ Frank K. Butler, LTC Andrew P. Cap,†† Mitchell Jay Cohen,‡‡ Ross Davenport,§§ Marc DePasquale,‖‖ Heidi Doughty,¶¶ Elon Glassberg,***††† Tor Hervig,‡‡‡ Timothy J. Hooper,§§§ Rosemary Kozar,‖‖‖ Marc Maegele,¶¶¶ Ernest E. Moore,**** Alan Murdock,†††† Paul M. Ness,‡‡‡‡ Shibani Pati,§§§§ Col Todd Rasmussen,‖‖‖‖ Anne Sailliol,¶¶¶¶ Martin A. Schreiber,***** Geir Arne Sunde,††††† Leo M. G. van de Watering,‡‡‡‡‡ Kevin R. Ward,§§§§§ Richard B. Weiskopf,‖‖‖‖‖ Nathan J. White,¶¶¶¶¶ Geir Strandenes,******††††† and Philip C. Spinella**‖‖‖‖‖‡‡‡‡‡**

**Department of Surgery, Mayo Clinic, Rochester, Minnesota; †Department of Surgery, Temple University School of Medicine, Philadelphia, Pennsylvania; ‡Transfusion Medicine, Blood Banking (American Society of Clinical Pathology), Netherlands Military Blood Bank; §Department of Transfusion Medicine, Örebro University Hospital, Örebro, Sweden; ‖Commander, US Army Institute of Surgical Research, San Antonio, Texas; ¶Trauma Sciences, Barts and the London School of Medicine, and Trauma & Vascular Surgery at the Royal London Hospital, London, UK; **Committee on Tactical Combat Casualty Care, Joint Trauma System, Joint Base San Antonio, Texas; ††Coagulation and Blood Research, US Army Institute of Surgical Research, JBSA Fort Sam Houston, Texas; ‡‡Department of Surgery University of California-San Francisco, San Francisco, California; §§Centre for Trauma Sciences, Blizard Institute, Bart's & the London School of Medicine, Queen Mary University of London, London, UK; ‖‖Deployment Medicine International, Gig Harbor, Washington; ¶¶Transfusion Medicine NHS Blood and Transplant, Birmingham, UK; ***The Trauma & Combat Medicine Branch, Surgeon General's HQ, Israel Defense Forces, Ramat Gan; and †††Department of Military Medicine, Hebrew University, Jerusalem, Israel; ‡‡‡Blood Bank, Haukeland University Hospital, and Department of Clinical Science, University of Bergen, Norway; §§§UK Defence Medical Services, Anaesthetic Department, Frenchay Hospital, Bristol UK; ‖‖‖Department of Surgery, Memorial Hermann Hospital, University of Texas Medical School at Houston, Houston, Texas; ¶¶¶Department for Traumatology, Orthopedic Surgery and Sportsmedicine Cologne–Merheim Medical Center, Cologne, Germany; ****Vice Chairman for Research, Department of Surgery, University of Colorado Denver, Colorado; ††††Surgeon General for Trauma, Air Force Medical Operations Agency, Lackland AFB, Texas; and Division of Trauma and General Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; ‡‡‡‡Transfusion Medicine Division, Johns Hopkins Medical Institutions, Baltimore, Maryland; §§§§Blood Systems Research Institute and University of California, San Francisco, California; ‖‖‖‖US Army Institute of Surgical Research, Joint Base San Antonio, Fort Sam Houston, Texas; ¶¶¶¶French Military Blood Transfusion Center, Clamart, France; *****Oregon Health & Science University, Portland, Oregon; †††††Norwegian Air Ambulance Foundation, Drøbak, Norway; ‡‡‡‡‡Sanquin Blood Supply, Center for Clinical Transfusion Research, Leiden, the Netherlands; §§§§§Michigan Center for Integrative Research in Critical Care, University of Michigan, Ann Arbor, Michigan; ‖‖‖‖‖Department of Anesthesia, University of California, San Francisco, California; ¶¶¶¶¶Division of Emergency Medicine, Department of Medicine, University of Washington, Seattle, Washington; ******Norwegian Naval Special Operation Commando and ††††††Department of Immunology and Transfusion Medicine, Haukeland University Hospital, Bergen, Norway; and ‡‡‡‡‡‡Division of Pediatric Critical Care, Department of Pediatrics, Washington University in St Louis, St Louis, Missouri*

Received 29 Oct 2013; first review completed 18 Nov 2013; accepted in final form 8 Jan 2014

Address reprint requests to Donald H. Jenkins, MD, Department of Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: jenkins.donald@mayo.edu.

Disclosures of interest: P.C.S.: TerumoBCT, Entegrion, Octapharma, grant recipient for NIH/NHLBI, US Department of Defense. E.E.M.: Grant recipient for US Department of Defense. R.D.: Grant recipient for TEM Innovations, Haemonetics. H.D.: UK Defence Medical Services. M.M.: Consultant for Biotest, CSL Behring, LFB, TEM International. P.M.N.: Consultant for TerumoBCT. J.F.R.: US Department of Defense. R.B.W.: NHLBI/NIH, FDA, US DOD, CaridianBCT, CSL-Behring. N.J.W.: National Institutes of Health NCCR-NCATS KL2 TR000421, Washington Life Sciences Discovery Fund, University of Washington Coulter Translational Research Award, and University of Washington Institute for Translational Health Sciences and is and is cofounder, board member, and consultant to Stasys Medical Corp and reports no conflicts of interest related to this work. Travel support for this work was provided by NIH NCCR-NCATS KL2 TR000421.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official, or as reflecting the views of the UK Defence Medical Services, US Army, US Department of Defense, Norwegian Armed Forces Medical Services, the French Armed Forces, Armed Forces of the Netherlands, Israel Defense Forces, or the Swedish Armed Forces.

DOI: 10.1097/SHK.0000000000000140

ABSTRACT—The Trauma Hemostasis and Oxygenation Research Network held its third annual Remote Damage Control Resuscitation Symposium in June 2013 in Bergen, Norway. The Trauma Hemostasis and Oxygenation Research Network is a multidisciplinary group of investigators with a common interest in improving outcomes and safety in patients with severe traumatic injury. The network's mission is to reduce the risk of morbidity and mortality from traumatic hemorrhagic shock, in the prehospital phase of resuscitation through research, education, and training. The concept of remote damage control resuscitation 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 prehospital phase of resuscitation is critical in these patients. If shock and coagulopathy can be rapidly identified and minimized before hospital admission, this will very likely reduce morbidity and mortality. 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.

KEYWORDS—Trauma, prehospital, transfusion, mortality, morbidity, resuscitation

ABBREVIATIONS—CWB — cold whole blood; DCR — damage control resuscitation; DIC — disseminated intravascular coagulation; EoT — endotheliopathy of trauma; FDP — freeze dried plasma; FFP — fresh frozen plasma; HIV — human immunodeficiency virus; NO — nitric oxide; PRT — pathogen reduction technique; RBCs — red blood cells; RDCR — remote damage control resuscitation; rFVIIa — recombinant human factor VIIa; TBI — traumatic brain injury; THOR — Trauma Hemostasis and Oxygenation Research; TTD — transfusion-transmitted disease; TXA — tranexamic acid

INTRODUCTION

The Trauma Hemostasis and Oxygenation Research (THOR) Network held its third annual Remote Damage Control Resuscitation (RDCR) Symposium in June 2013 at Solstrand Hotel, near Bergen Norway. The THOR Network 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 prehospital phase of resuscitation through education, training, and research.

Remote damage control resuscitation has been defined as the prehospital application of damage control resuscitation (DCR) concepts (1, 2). Damage control resuscitation 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 US 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 (3), states "DCR addresses the entire lethal triad immediately upon admission to a combat hospital." Others have promoted expanding the definition to include care from the point of injury (5). Because early identification and treatment of hemorrhagic shock may improve outcomes, we contend that the distinction between RDCR and DCR is an important one because there are differences in capabilities and, in some cases, optimal management strategies between prehospital 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 prehospital resuscitation concepts and others discussed at the RDCR symposia in the past has motivated the leadership to produce a position paper. The aim of this article was 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 also 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 are 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 blood 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 proteins 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 pathophysiological 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 prothrombotic environment. In complex pathophysiological conditions, due to severe traumatic injury and resuscitation, both hypocoagulable 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 hypercoagulable to hypocoagulable or hypohypercoagulable 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, and trauma-induced coagulopathy (TIC).

Acute traumatic coagulopathy 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 proinflammatory signaling, in addition to many other unknown pathways. *Trauma-induced coagulopathy* is a broader term that has been used to describe both endogenous (primary) and exogenous (secondary) causes of coagulopathy following trauma. Although 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, is 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 among 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), 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* include all exogenous or iatrogenic causes of coagulopathy. The characterization of this secondary coagulopathy will be difficult because 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 (*a*) coagulation, (*b*) inflammation, (*c*) blood-organ endothelial barrier integrity, and (*d*) 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, von Willebrand factor, syndecans (surrogates for injury to the glycocalyx), soluble P-selectin, soluble E-selectin, soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1, tissue factor, endothelin 1, homocysteine, endothelial NO synthase, plasminogen activator inhibitor 1, superoxide dismutase, and tissue plasminogen activator (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. Preclinical 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.

Lifesaving 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 prehospital 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 such as 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 more than 60 min from wounding until reaching a medical treatment facility that is capable of providing damage control surgery and DCR. The term *prolonged* evacuation will be defined as more than 6 h from point of wounding until arrival at a medical treatment facility capable of providing damage control surgery. These definitions apply equally to both civilian and military environments. Although 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 procoagulants. 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 such as plasma derivatives, such as solvent detergent–treated plasma or lyophilized plasma products, fibrinogen, prothrombin complex concentrates (PCCs), 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 2 primary categories: (*a*) *labile blood products* and (*b*) *biological medications* derived from plasma by fractionation and concentration techniques.

Labile blood products are obtained by separation of whole blood into plasma, RBCs, 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* is used when the blood is maintained at 22°C to 26°C after donation. If the donated blood is cooled to 2°C to 6°C, it is referred to as *cold whole blood* (CWB). Whole blood stored for less than 48 h 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 or solvent detergent plasma, 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.

End points of resuscitation

Reestablishing adequate end-organ perfusion, restoring normal coagulation, and repaying oxygen debt are the essential end points of resuscitation. Rudimentary assessment of the end points 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 end points of fluid resuscitation, although few data are available to support their use. No attempt is made to establish adequacy of tissue perfusion using any sort of device or laboratory test because of 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 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) O_2 and/or CO_2 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

Prehospital 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 prehospital setting (34). Packed RBCs 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, offer the potential for blood products to be administered in the prehospital 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 prehospital and remote settings. Currently, plasma is available for casualty care in Afghanistan at the roles 2 and 3 fixed hospitals (German and French), and FDP is carried by U.S. 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 prehospital setting for RDCR.

Use of whole blood

Based on the current literature, our position is that whole blood should be used for lifesaving 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 immunoglobulin M and 400 for immunoglobulin G. For nonemergency 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 are 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 widespread 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 (TTDs), but this may not be possible because of logistical constraints.

Current options for maximizing blood safety include the use of pretested donors and rapid testing at the time of donation. The following steps to minimize whole blood TTD risks should be considered (37). Before deployment, all personnel should undergo immunization against hepatitis B virus and, if possible, screening for human immunodeficiency virus (HIV). Volunteer blood donors should be screened and fully tested for TTDs at a minimum in compliance with World Health Organization standards. Blood samples should be sent to laboratories for nucleic acid testing for HIV, hepatitis B virus surface antigen, hepatitis C virus, 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, malaria, dengue, and Chagas disease. Donor testing, although logistically challenging, should be repeated at pre–agreed-upon intervals such as every 90 to 180 days (39).

Pretesting for members of small units operating in austere environments can maximize number of donors for buddy transfusions. Rapid tests exist for HIV, hepatitis B virus surface antigen, hepatitis C virus, syphilis (rapid plasma reagin), 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 laboratories.

Transfusion-transmitted disease 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 antimalarial 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 (PRTs) 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. Although 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 because of the lack of evidence supporting this strategy, patients should never be overresuscitated 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 antifibrinolytic TXA, administered upon admission to hospital within 3 h of injury, reduced all-cause mortality and death due to hemorrhage in trauma patients without an increase in venous thromboembolism (49, 50). Similar findings were reported in the MATTERS-2 study of combat casualties in Afghanistan, although a higher rate of venous thromboembolism 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 prehospital 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 approach to the use of TXA as part of a protocol for the resuscitation of patients in hemorrhagic shock (54).

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 (55–57). 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 (58, 59). In a large population study of severely injured patients, the early use of fibrinogen concentrate was associated with significantly lower 6-h mortality and an increased time to death, but also an increased rate of multiple organ failure (60). Randomized trials, particularly in the prehospital setting, are urgently needed to guide appropriate use of this promising agent in trauma resuscitation.

Improvement of thrombin generation—Recombinant human factor VIIa has been evaluated as a hemostatic adjunct in trauma and in other bleeding patients. While rFVIIa likely reduces bleeding and RBC 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) (61, 62). Its use in trauma as a hemostatic adjunct cannot be recommended outside a clinical trial setting.

Prothrombin complex concentrates have become the new standard of care in managing hemorrhage in the setting of warfarin anticoagulation (63). Their use in a broader population of trauma patients has not been evaluated adequately in randomized controlled trials. Animal studies suggest that PCCs may be useful in reducing blood loss but may also increase the risk of developing DIC (64, 65). 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 used 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 (66). More recently, junctional tourniquets have been used with specific direction for training and use, but evidence of their effectiveness in RDCR has yet to be established (67). Control of "noncompressible" 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 that 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

Prehospital monitoring of shock and coagulopathy

Prehospital 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) (68, 69). But even if these are normal or close to normal, shock at the cellular or organ level may still be present (70, 71). Options for real-time physiological assessment and optimum hemodynamic monitoring including coagulation during prehospital resuscitation are

limited by logistics, cost, and training. Advanced point-of-care 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 point-of-care 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 because a large proportion of patient evacuations are greater than 1 h.

End points for resuscitation

While hospital-based end points are dependent on 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. Even though it is used within the London Helicopter Emergency Medical Service and Norwegian Air Ambulance systems, it is unknown if the use of ultrasound of the vena cava as an estimate of intravascular volume can improve outcomes in an RDCR environment. Is there a combination of endpoints of resuscitation that can best define that resuscitation has been successful or needs to continue? In the setting of hypotensive resuscitation, are the parameters for setting end points 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 premission/preinjury? Is resolution of coagulopathy an 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 end points of prehospital shock resuscitation.

Whole blood compared with 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 (72). Unfortunately, because 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 with 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 randomized controlled trials analyzing the efficacy of warm and cold whole blood in patients requiring cardiac surgery have demonstrated mixed results (73–78). With the resurgence of interest in the hemostatic effect of platelet-containing products stored at 2°C to 6°C, there is also renewed interest in performing trials comparing CWB, stored at 2°C to 6°C for up to 10 days, with reconstituted whole blood from blood components. These trials are very important to perform because 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 with storage under refrigeration, the standard of care until the 1980s (43, 79–81). The need for a practical way to provide hemostatically functional platelets to support RDCR suggests that platelet and whole blood refrigeration should be reexamined. 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 (82). There are several fundamental questions that need to be answered. Are lyophilized 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 versus freeze drying affect 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 "reconstitute whole blood"), in addition to the effect on combining lyophilized 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 (83–86). Processing methods for plasma include amotosalen, solvent detergent treatment, nanofiltration, methylene blue, and UV light with riboflavin. Pathogen reduction techniques 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 on their processing methods may offer additional benefits including (*a*) reducing microparticle

and WBC loads that appear to promote immunomodulation and a prothrombotic state, (*b*) pooling of plasma donors that appears to reduce the risk of transfusion-related acute lung injury, and (*c*) pooling of plasma donors that produces a consistent product regarding coagulation factors compared with 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 are poorly understood but include a combination of both hypocoagulable and hypercoagulable states promoted by the magnitude of the brain tissue injured (87). The underlying mechanisms may comprise the release of tissue factor, hyperfibrinolysis, shock, and hypoperfusion, thus triggering the protein C pathway, DIC, and platelet dysfunction (88). 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

(a) examine the feasibility of prehospital transfusion and hemostatic use;
(b) highlight what potential patient populations may benefit most from specific interventions;
(c) suggest what prehospital strategies may hold most benefit;
(d) provide large data set to answers questions regarding unique types of situations or patients;
(e) provide support for investigator-initiated study;
(f) inform future clinical trials of prehospital hemostatic use; and
(g) 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 handoffs. 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 the following: (*a*) cluster randomization (based on 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 (89); (*b*) sequential analyses: with every end point 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 (90, 91).

CONCLUSIONS

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 prehospital phase of their resuscitation is critical, and if shock and coagulopathy can be rapidly identified and corrected before 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.

REFERENCES

1. Gerhardt RT, Berry JA, Blackbourne LH: Analysis of life-saving interventions performed by out-of-hospital combat medical personnel. *J Trauma* 71(Suppl 1):S109–S113, 2011.
2. Strandenes G, Spinella PC: The Solstrand remote damage control resuscitation symposium. *Transfusion* 53(Suppl 1):6S–8S, 2013.
3. Holcomb JB, Jenkins D, Rhee P, Johannigman J, Mahoney P, Mehta S, Cox ED, Gehrke MJ, Beilman GJ, Schreiber M, et al.: Damage control resuscitation: directly addressing the early coagulopathy of trauma. *J Trauma* 62(2): 307–310, 2007.
4. Gerhardt RT, Strandenes G, Cap AP, Rentas FJ, Glassberg E, Mott J, Dubick MA, Spinella PC, THOR Network, RemTorn Study Groups: Remote damage control resuscitation and the Solstrand Conference: defining the need, the language, and a way forward. *Transfusion* 53(Suppl 1):9S–16S, 2013.
5. Hodgetts TJ, Mahoney PF, Kirkman E: Damage control resuscitation. *J R Army Med Corps* 153(4):299–300, 2007. Published online ahead of print 1964/02/01.
6. Barbee RW, Reynolds PS, Ward KR: Assessing shock resuscitation strategies by oxygen debt repayment. *Shock* 33(2):113–122, 2010.
7. Crowell JW, Smith EE: Oxygen deficit and irreversible hemorrhagic shock. *Am J Physiol* 206:313–316, 1964.
8. Rixen D, Siegel JH: Bench-to-bedside review: oxygen debt and its metabolic correlates as quantifiers of the severity of hemorrhagic and post-traumatic shock. *Crit Care* 9(5):441–453, 2005.
9. Shoemaker WC, Appel PL, Kram HB: Tissue oxygen debt as a determinant of lethal and nonlethal postoperative organ failure. *Crit Care Med* 16(11): 1117–1120, 1988.
10. White NJ, Martin EJ, Brophy DF, Ward KR: Coagulopathy and traumatic shock: characterizing hemostatic function during the critical period prior to fluid resuscitation. *Resuscitation* 81(1):111–116, 2010.

11. Siegel JH, Fabian M, Smith JA, Kingston EP, Steele KA, Wells MR, Kaplan LJ: Oxygen debt criteria quantify the effectiveness of early partial resuscitation after hypovolemic hemorrhagic shock. *J Trauma* 54(5):862–880, 2003; discussion 880.
12. Hoffman M, Monroe DM: Coagulation 2006: a modern view of hemostasis. *Hematol Oncol Clin North Am* 21(1):1–11, 2007.
13. Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M: Newer concepts of blood coagulation. *Haemophilia* 4(4):331–334, 1998.
14. Versteeg HH, Heemskerk JW, Levi M, Reitsma PH: New fundamentals in hemostasis. *Physiol Rev* 93(1):327–358, 2013.
15. Wohlauer MV, Moore EE, Thomas S, Sauaia A, Evans E, Harr J, Silliman CC, Ploplis V, Castellino FJ, Walsh M: Early platelet dysfunction: an unrecognized role in the acute coagulopathy of trauma. *J Am Coll Surg* 214(5):739–746, 2012.
16. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K: Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes. *J Thromb Haemost* 10(7):1342–1351, 2012.
17. Tanaka KA, Key NS, Levy JH: Blood coagulation: hemostasis and thrombin regulation. *Anesth Analg* 108(5):1433–1446, 2009.
18. Carey JS: Physiological hemodilution: interrelationships between hemodynamics and blood volume after acute blood loss. *Ann Surg* 178(1):87–94, 1973.
19. Prist R, Rocha-e-Silva M, Scalabrini A, Coelho IJ, Franca ES, Meneghetti C, Braga GA: A quantitative analysis of transcapillary refill in severe hemorrhagic hypotension in dogs. *Shock* 1(3):188–195, 1994.
20. Isbister JP: Physiology and pathophysiology of blood volume regulation. *Transfus Sci* 18(3):409–423, 1997.
21. Engelmann B, Massberg S: Thrombosis as an intravascular effector of innate immunity. Nature reviews Immunology. 13(1):2013, 34–45.
22. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF: Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? *Ann Surg* 245(5):812–818, 2007.
23. Kashuk JL, Moore EE, Sawyer M, Wohlauer M, Pezold M, Barnett C, et al.: Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. *Ann Surg* 252(3):434–442, 2010; discussion 443–444.
24. Nachman RL, Rafii S: Platelets, petechiae, and preservation of the vascular wall. *N Engl J Med* 359(12):1261–1270, 2008.
25. Peng Z, Pati S, Potter D, Brown R, Holcomb JB, Grill R, Wataha K, Park PW, Xue H, Kozar RA: Fresh frozen plasma lessens pulmonary endothelial inflammation and hyperpermeability after hemorrhagic shock and is associated with loss of syndecan 1. *Shock* 40(3):195–202, 2013.
26. Pati S, Matijevic N, Doursout MF, Ko T, Cao Y, Deng X, Kozar RA, Hartwell E, Conyers J, Holcomb JB: Protective effects of fresh frozen plasma on vascular endothelial permeability, coagulation, and resuscitation after hemorrhagic shock are time dependent and diminish between days 0 and 5 after thaw. *J Trauma* 69(Suppl 1):S55–S63, 2010.
27. Kozar RA, Peng Z, Zhang R, Holcomb JB, Pati S, Park P, Ko TC, Paredes A: Plasma restoration of endothelial glycocalyx in a rodent model of hemorrhagic shock. *Anesth Analg* 112(6):1289–1295, 2011.
28. Hakre S, Manak MM, Murray CK, Davis KW, Bose M, Harding AJ, Maas PR, Jagodzinski LL, Kim JH, Michael NL, et al.: Transfusion-transmitted human T-lymphotropic virus Type I infection in a United States military emergency whole blood transfusion recipient in Afghanistan, 2010. *Transfusion* 53(10): 2176–2182, 2013. Published online ahead of print 2013/02/01.
29. Wataha K, Menge T, Deng X, Shah A, Bode A, Holcomb JB, Potter D, Kozar R, Spinella PC, Pati S: Spray-dried plasma and fresh frozen plasma modulate permeability and inflammation *in vitro* in vascular endothelial cells. *Transfusion* 53(Suppl 1):80S–90S, 2013. Published online ahead of print 2013/02/21.
30. Spinella PC, Holcomb JB: Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev* 23(6):231–240, 2009. Published online ahead of print 2009/08/22.
31. Demetriades D, Kimbrell B, Salim A, Velmahos G, Rhee P, Preston C, Gruzinski G, Chan L: Trauma deaths in a mature urban trauma system: is "trimodal" distribution a valid concept? *J Am Coll Surg* 201(3):343–348, 2005.
32. Brenner ML, Moore LJ, Dubose JJ, Tyson GH, McNutt MK, Albarado RP, Holcomb JB, Scalea TM, Rasmussen TE: A clinical series of resuscitative endovascular balloon occlusion of the aorta for hemorrhage control and resuscitation. *J Trauma Acute Care Surg* 75(3):506–511, 2013. Published online ahead of print 2013/10/04.
33. Kotwal RS, Montgomery HR, Kotwal BM, Champion HR, Butler FK Jr, Mabry RL, Cain JS, Blackbourne LH, Mechler KK, Holcomb JB: Eliminating preventable death on the battlefield. *Arch Surg* 146(12):1350–1358, 2011.
34. Hooper T, Nadler R, Badloe J, Butler FK, Glassberg E: Implementation and execution of military remote damage control resuscitation programs. *Shock* 41(Suppl):90–97, 2014.
35. Arav A, Natan D: Freeze drying (lyophilization) of red blood cells. *J Trauma* 70(Suppl 5):S61–S64, 2011.
36. Glassberg E, Nadler R, Gendler S, Abramovich A, Spinella PC, Gerhardt RT, Holcomb JB, Kreiss Y: Freeze dried plasma at the point of injury—from concept to doctrine. *Shock* 40(6):444–450, 2013.
37. Berseus O, Boman K, Nessen SC, Westerberg LA: Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. *Transfusion* 53(Suppl 1):114S–123S, 2013.
38. Strandenes G, De Pasquale M, Cap AP, Hervig TA, Kristoffersen E, Hickey M, Cordova C, Berseus O, Eliassen HS, Fisher L, et al.: Emergency whole blood use in the field: a simplified protocol for collection and transfusion. *Shock* 41(Suppl):76-83, 2014.
39. Hakre S, Peel SA, O'Connell RJ, Sanders-Buell EE, Jagodzinski LL, Eggleston JC, Myles O, Waterman PE, McBride RH, Eader SA, et al.: Transfusion-transmissible viral infections among US military recipients of whole blood and platelets during Operation Enduring Freedom and Operation Iraqi Freedom. *Transfusion* 51(3): 473–485, 2011.
40. Joint Theater Trauma System Clinical Practice Guideline 2012. Available at: http://www.usaisr.amedd.army.mil/assets/cpgs/Fresh_Whole_Blood_Transfusion_24_Oct_12.pdf. Accessed November 1, 2013.
41. Spinella PC, Reddy HL, Jaffe JS, Cap AP, Goodrich RP: Fresh whole blood use for hemorrhagic shock: preserving benefit while avoiding complications. *Anesth Analg* 115(4):751–758, 2012.
42. Prat N, Pidcoke HF, Sailliol A, Cap AP: Evolution of US military transfusion support for resuscitation of trauma and hemorrhagic shock [translated from french]. *Transfus Clin Biol* 20(2):225–230, 2013.
43. Pidcoke HF, McFaul SJ, Ramasubramanian AK, Parida BK, Mora AG, Fedyk CG, Valdez-Delgado KK, Montgomery RK, Reddoch KM, Rodriguez AC, et al.: Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. *Transfusion* 53(Suppl 1): 137S–149S, 2013.
44. Bickell WH, Wall MJ Jr, Pepe PE, Martin RR, Ginger VF, Allen MK, Mattox KL: Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med* 331(17):1105–1109, 1994.
45. Dutton RP, Mackenzie CF, Scalea TM: Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. *J Trauma* 52(6):1141–1146, 2002.
46. Morrison CA, Carrick MM, Norman MA, Scott BG, Welsh FJ, Tsai P, Liscum KR, Wall MJ Jr, Mattox KL: Hypotensive resuscitation strategy reduces transfusion requirements and severe postoperative coagulopathy in trauma patients with hemorrhagic shock: preliminary results of a randomized controlled trial. *J Trauma* 70(3):652–663, 2011.
47. Cannon W, Frasen J, Cowel E: The preventive treatment of wound shock. *JAMA* 70:618–621, 1918.
48. Eastridge BJ, Mabry RL, Blackbourne LH, Butler FK: We don't know what we don't know: prehospital data in combat casualty care. *US Army Med Dep J* 2011(Apr–Jun):11–14, 2011.
49. Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, et al.: Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 376(9734):23–32, 2010.
50. Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, Dewan Y, Gando S, Guyatt G, Hunt BJ, Morales C, et al.: The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet* 377(9771):1096–1101, 2011, 101e1–101e2.
51. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ: Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study. *Arch Surg* 147(2):113–119, 2012.
52. de Guzman R, Polykratis IA, Sondeen JL, Darlington DN, Cap AP, Dubick MA: Stability of tranexamic acid after 12-week storage at temperatures from –20 degrees C to 50 degrees C. *Prehosp Emerg Care* 17(3):394–400, 2013.
53. Lipsky AM, Abramovich A, Nadler R, Feinstein U, Shaked G, Kreiss Y, Glassberg E: Tranexamic acid in the prehospital setting: Israel Defense Forces' initial experience. *Injury* 45(1):66–70, 2014.
54. NATO Medical Blood Advisory Team. The use of tranexamic acid (TXA) in bleeding combat casualties. Brussels, Belgium: NATO; 2013.
55. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, Levrat A, Guillaume C, Marcotte TM, Vulliez A, et al.: Early coagulopathy in trauma patients: an on-scene and hospital admission study. *Injury* 43(1):26–32, 2012.
56. Darlington DN, Craig T, Gonzales MD, Schwacha MG, Cap AP, Dubick MA: Acute coagulopathy of trauma in the rat. *Shock* 39(5):440–446, 2013.
57. Schlimp CJ, Voelckel W, Inaba K, Maegele M, Ponschab M, Schochl H: Estimation of plasma fibrinogen levels based on hemoglobin, base excess and Injury Severity Score upon emergency room admission. *Crit Care* 17(4): R137, 2013.
58. Schochl H, Schlimp CJ: Trauma bleeding management: the concept of goal-directed primary care. *Anesth Analg* 2013. Published online ahead of print 2013/06/13.

59. Rahe-Meyer N, Solomon C, Hanke A, Schmidt DS, Knoerzer D, Hochleitner G, Sorensen B, Hagl C, Pichlmaier M: Effects of fibrinogen concentrate as first-line therapy during major aortic replacement surgery: a randomized, placebo-controlled trial. *Anesthesiology* 118(1):40–50, 2013. Published online ahead of print 2012/12/20.
60. Wafaisade A, Lefering R, Maegele M, Brockamp T, Mutschler M, Lendemans S, Banerjee M, Bouillon B, Probst C, Trauma Registry of D. G. U: Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. *J Trauma Acute Care Surg* 74(2):387–393, 2013; discussion 393–395.
61. Lin Y, Stanworth S, Birchall J, Doree C, Hyde C: Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. *Cochrane Database Syst Rev* (2):CD005011, 2011.
62. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, Sundaram V, McMahon D, Olkin I, McDonald KM, et al.: Systematic review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Ann Intern Med* 154(8):529–540, 2011.
63. Patriquin C, Crowther M: Treatment of warfarin-associated coagulopathy with vitamin K. *Expert Rev Hematol* 4(6):657–665, 2011; quiz 666–667.
64. Honickel M, Rieg A, Rossaint R, Braunschweig T, Spronk HM, ten Cate H, van Oerle R, Tolba R, Grottke O: Prothrombin complex concentrate reduces blood loss and enhances thrombin generation in a pig model with blunt liver injury under severe hypothermia. *Thromb Haemost* 106(4):724–733, 2011.
65. Grottke O, Braunschweig T, Spronk HM, Esch S, Rieg AD, van Oerle R, ten Cate H, Fitzner C, Tolba R, Rossaint R: Increasing concentrations of prothrombin complex concentrate induce disseminated intravascular coagulation in a pig model of coagulopathy with blunt liver injury. *Blood* 118(7): 1943–1951, 2011.
66. Kragh JF Jr, Walters TJ, Baer DG, Fox CJ, Wade CE, Salinas J, Holcomb JB: Practical use of emergency tourniquets to stop bleeding in major limb trauma. *J Trauma* 64(Suppl 2):S38–S49, 2008; discussion S50.
67. Comat Ready Clamp Addition to the Tactical Combat Casualty Care Guidelines 2011-07 2011. Available at: http://www.health.mil/Libraries/110808_TCCC_Course_Materials/0762-DHB-Memo-110923-Combat-Ready-Clamp.pdf. Accessed October 1, 2013.
68. Adams HA, Baumann G, Gansslen A, Janssens U, Knoefel W, Koch T, et al.: Definition of shock types [translated from German]. *Anasthesiol Intensivmed Notfallmed Schmerzther* 36(Suppl 2):S140–S143, 2001.
69. Jousi M, Reitala J, Lund V, Katila A, Leppaniemi A: The role of pre-hospital blood gas analysis in trauma resuscitation. *World J Emerg Surg* 5:10, 2010.
70. Dabrowski GP, Steinberg SM, Ferrara JJ, Flint LM: A critical assessment of endpoints of shock resuscitation. *Surg Clin North Am* 80(3):825–844, 2000.
71. McKinley BA, Valdivia A, Moore FA: Goal-oriented shock resuscitation for major torso trauma: what are we learning? *Curr Opin Crit Care* 9(4):292–299, 2003.
72. Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, Hobbs R, Scroggins J, Hartwell B, Kozar RA, et al.: A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. *Ann Surg* 258(4):527–532, 2013; discussion 532–533.
73. Manno CS, Hedberg KW, Kim HC, Bunin GR, Nicolson S, Jobes D, Schwartz E, Norwood WI: Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood* 77(5):930–936, 1991.
74. Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F, Town DA, Roy LC, Scott W, Stromberg D: Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. *N Engl J Med* 351:1635–1644, 2004.
75. Becker GA, Tuccelli M, Kunicki T, Chalos MK, Aster RH: Studies of platelet concentrates stored at 22 C nad 4 C. *Transfusion* 13(2):61–68, 1973.
76. Ho AMKM, Dion PW: Are we giving enough coagulation factors during major trauma resuscitation? *Am J Surg* 190:479–484, 2005.
77. Perkins JG, Cap AP, Spinella PC, Shorr AF, Beekley AC, Grathwohl KW, Rentas FJ, Wade CE, Holcomb JB: Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients (CME). *Transfusion* 51(2):242–252, 2011.
78. Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB: Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. *J Trauma* 66(Suppl 4):S69–S76, 2009.
79. Palavecino EL, Yomtovian RA, Jacobs MR: Bacterial contamination of platelets. *Transfus Apher Sci* 42(1):71–82, 2010.
80. Montgomery RK, Reddoch KM, Evani SJ, Cap AP, Ramasubramanian AK: Enhanced shear-induced platelet aggregation due to low-temperature storage. *Transfusion* 53(7):1520–1530, 2013.
81. Jobes D, Wolfe Y, O'Neill D, Calder J, Jones L, Sesok-Pizzini D, Zheng XL: Toward a definition of "fresh" whole blood: an *in vitro* characterization of coagulation properties in refrigerated whole blood for transfusion. *Transfusion* 51(1):43–51, 2011.
82. Schmidt PJ: The plasma wars: a history. *Transfusion* 52(Suppl 1):2S–4S, 2012.
83. Klein HG: Pathogen inactivation technology: cleansing the blood supply. *J Intern Med* 257(3):224–237, 2005.
84. Marschner S, Fast LD, Baldwin WM 3rd, Slichter SJ, Goodrich RP: White blood cell inactivation after treatment with riboflavin and ultraviolet light. *Transfusion* 50(11):2489–2498, 2010.
85. Krusius T, Auvinen MK, Tuimala J: Introduction of Octaplas in clinical use decreased the rate of serious adverse reactions. *Vox Sang* 99(Suppl 1):P–1018, 2010.
86. Hellstern P, Solheim BG: The use of solvent/detergent treatment in pathogen reduction of plasma. *Transfus Med Hemother* 38(1):65–70, 2011.
87. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI: Coagulation disorders after traumatic brain injury. *Acta Neurochir* 150(2):165–175, 2008; discussion 175.
88. Maegele M: Coagulopathy after traumatic brain injury: incidence, pathogenesis, and treatment options. *Transfusion* 53(Suppl 1):28S–37S, 2013.
89. Hahn S, Puffer S, Torgerson DJ, Watson J: Methodological bias in cluster randomised trials. *BMC Med Res Methodol* 5:10, 2005.
90. Groeneveld GJ, Graf M, van der Tweel I, van den Berg LH, Ludolph AC: Alternative trial design in amyotrophic lateral sclerosis saves time and patients. *Amyotroph Lateral Scler* 8(5):266–269, 2007.
91. Newton DR, Tanner JM: *N*-acetylpara-aminophenol as an analgesic; a controlled clinical trial using the method of sequential analysis. *Br Med J* 2(5001): 1096–1099, 1956.