**PROTOCOL TITLE:** Plasma Resuscitation without Lung Injury (PROPOLIS)

**SECTION A: RESEARCH TEAM AND LOCATIONS**

**A1. RESEARCH TEAM**

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| **Study Role** | **Institution/Company and Contact Information** | | |
| **Sponsor** | | *Organization/Institution/Company:* Coalition for National Trauma Research (CNTR)  *Address:* Colonnade 1, 9901 IH 10 West, Suite 720, San Antonio, TX 78230  *Point of Contact:*  *Name and Degree:* Monica Phillips  *Title:* Senior Program Manager  *Phone Number:* 210-455-8038  *Email:* Monica@NatTrauma.org | | |
| **Principal Investigator** | | *Name, Rank, and Degree:* Leopoldo C. Cancio, MD  *Title:* Director  *Institution:* U.S. Army Burn Center  *Address:* 3698 Chambers Pass, Fort Sam Houston, TX 78234-6315  *Phone Number:* 210-916-0990  *Email:* Leopoldo.c.cancio.civ@mail.mil | | |
| **Associate Investigator(s)** | | | *Name, Rank, and Degree:* Steven Wolf, MD, FACS  *Title: Professor and Chief, Divison of Burn and Trauma Surgery*  *Institution/Company: University of Texas Medical Branch Shriners Burns Hospitals for Children*  *Address: 815 Market Street, Galveston, TX 77550-2725*  *Phone Number: 409-770-6607*  *Email: swolf@utmb.edu*  *Name, Rank, and Degree:* Barclay Stewart, MD, PhD, MscPH  *Title:* Assistant Professor, Trauma, Critical Care, and Burn, University of Washington School of Medicine  *Institution/Company:* Harborview Medical Center  *Address:* Mailbox 359796  325 Ninth Avenue  Seattle, Washington 98104-2499  *Phone Number:* (206) 744-3140  *Email:* barclays@uw.ecu  *Name, Rank, and Degree:* Nicole S. Gibran, MD, FACS  *Title:* Associate Dean for Research and Graduate Education; Professor, Department of Surgery, University of Washington  *Institution/Company:* Harborview Medical Center  *Address:* Box 359796  325 Ninth Avenue  Seattle, WA 98104  *Phone Number:* 206 744-3140  *Email:* nicoleg@uw.edu | | |
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| **Research Monitor** | | | *Name, Rank, and Degree: Dr. Kevin Chung, MD*  *Title: Chair,* Department of Medicine  *Institution/Company:* Uniformed Services University of the Health Sciences  *Address: 4301 Jones Bridge Road*  Bethesda, MD, 20814  *Phone Number: (301) 205-2010*  *Email:* kevin.chung@usuhs.edu | | | |
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| **Consultants** (Subject  Matter Experts, others) | *Name, Rank, and Degree:* Laurence Corash, MD  *Title:* Chief Medical Officer  *Institution/Company:* Cerus Corporation  *Address:* 1220 Concord Avenue - Suite 600  Concord, CA 94520.  *Phone Number:* 925-288-6118  *Email:* [lcorash@cerus.com](mailto:lcorash@cerus.com)  *Name, Rank, and Degree*:  *Insitution/Company*: The Blood Center  *Address*: 1116 McKaskle Dr.  Hammond, LA 70403  *Phone Number*: 985-340-2320  *Email*: |

**A2. ROLES AND RESPONSIBILITIES**

**A2.1 Key Research Personnel**

*Name(s):* Leopoldo C. Cancio

*Research Role:* Principal Investigator (PI); Site PI at the USAISR site.

*Study Responsibilities:* Overall management of the protocol. Enroll patients and conduct study at the USAISR site.

*Name(s):* Steve Wolf

*Research Role:* Site PI, University of Texas Medical Branch (UTMB)

*Study Responsibilities:* Enroll patients and conduct study at the UTMB site.

*Name(s):* Barclay Stewart

*Research Role:* Site PI, University of Washington

*Study Responsibilities:* Enroll patients and conduct study at the University of Washington site.

*Name(s):* Jan Jansen

*Research Role:* Site PI, University of Alabama at Birmingham (UAB) site

*Study Responsibilities:* Enroll patients and conduct study at the UAB site.

*Name(s):* Robel Beyene

*Research Role:* Site PI, Vanderbilt University (VUMC)

*Study Responsibilities:* Enroll patients and conduct study at the VUMC site.

Name(s): Samuel P. Mandell

Research Role: Site PI, UT Southwestern (UTSW)

Study Responsibilities: Enroll patinetns and conduct study at the UTSW site.

*Name(s):* Rosemary Kozar

*Research Role:* Associate Investigator, University of Maryland

*Study Responsibilities:* Perform assays in support of study objectives.

*Name(s):* James Bynum

*Research Role:* Associate Investigator, USAISR

*Study Responsibilities:* Perform assays in support of study objectives.

*Name(s):* Nicole Gibran

*Research Role:* Coordinating Principal Investigator

*Study Responsibilities:* Assist the PI in overall execution of the study.

*Name(s):* Dagmar Amtmann

*Research Role:* Statistician

*Study Responsibilities:* Database management and statistical support for the study.

**A2.2. Others Involved in the Research, as applicable**

*Name(s):* Monica Phillips, Coalition for National Trauma Research

*Research Role:* Senior Program Manager

*Study Responsibilities:* Manage administrative aspects of study execution.

**A3. RESEARCH LOCATIONS**

1. U.S. Army Institute of Surgical Research, Fort Sam Houston, TX
2. Regional Burn Center at Harborview, University of Washington, Seattle, WA
3. University of Texas Medical Branch, Galveston, TX
4. University of Maryland School of Medicine, Baltimore, MD
5. Vanderbilt University Medical Center, Nashville, TN
6. University of Alabama at Birmingham, Birmingham, AL
7. University of Texas Southwestern, Dallas, TX

**A4. MULTISITE RESEARCH**

***Lead Site****:* U.S. Army Institute of Surgical Research

*Lead Site Investigator:* Leopoldo C. Cancio, MD, FACS

*IRB that will review for the lead site:* Western IRB

*Function/Role of Lead Site*: Overall study coordination. Perform certain assays (James Bynum, PhD) Will also enroll patients as a participating site.

***Performance******Site****:* Regional Burn Center at Harborview, University of Washington, Seattle, WA

*Performance Site Investigator*: Barclay Stewart, MD, FACS

*IRB that will review for the Performance Site*:

*Function/Role of Performance Site*: Enroll patients as a participating site

***Performance******Site****:* University of Texas Medical Branch

*Performance Site Investigator*: Steven Wolf, MD, FACS

*IRB that will review for the Performance Site*: Western IRB

*Function/Role of Performance Site*: Enroll patients as a participating site

***Performance******Site****:* University of Maryland School of Medicine, Baltimore, MD

*Performance Site Investigator*: Rosemary Kozar, MD, FACS

*IRB that will review for the Performance Site*: Western IRB

*Function/Role of Performance Site*: Laboratory assays; no patient enrollments

***Performance******Site****:* Vanderbilt Burn Center, Nashville, TN

*Performance Site Investigator*: Robel Beyenne, MD, FACS

*IRB that will review for the Performance Site*: Western IRB

*Function/Role of Performance Site*: Enroll patients as a participating site

***Performance******Site****:* University of Alabama at Birmingham, Birmingham, AL

*Performance Site Investigator*: Jan Jansen, MBBS, PhD

*IRB that will review for the Performance Site*: Western IRB

*Function/Role of Performance Site*: Enroll patients as a participating site

***Performance******Site****:* University of Texas Southwestern, Dallas, TX

*Performance Site Investigator*: Sameul Mandell, MD, FACS

*IRB that will review for the Performance Site*: Western IRB

*Function/Role of Performance Site*: Enroll patients as a participating site

**SECTION B: RESEARCH METHODOLOGY**

**B1. ABSTRACT**

Purpose: The treatment of patients with major burns requires resuscitation with large amounts of fluid, typically a crystalloid solution that is given by vein (i.v.). This treatment is needed in order to restore circulating blood volume. But it also leads to edema formation in the tissues, which may cause injury to vital organs, especially the lungs and kidneys, and even in death. In this study, we propose to use pathogen-reduced plasma (PRP), an FDA-approved blood component that has undergone special treatment to reduce the risk of disease transmission. We aim to: 1) reduce the amount of fluid given during the first 24 hours after a burn and 2) reduce the incidence of lung injury and other complications related to the administration of fluids. We also aim to determine if the blood product has any effect on inflammation. An overall decrease in the amount of fluids that burn patients receive should decrease the potential for lung injury, decrease days in the hospital, and improve survival.

Subject Population: Adult patients admitted to (and enrollable at) an ABA-verified burn center within 8 hours of sustaining a burn injury > 20% total body surface area (TBSA) and undergoing intravenous fluid resuscitation for at least 24 hours, will be enrolled and randomized. This study will enroll 94 subjects (47 per group) at 5 participating centers (19 subjects per site) over 3 years.

Study Design: This is an open-label, prospective, randomized, controlled, multicenter clinical trial. The control group will receive standard crystalloid resuscitation, while the treatment group will receive 1mL/kg/%burn of pathogen-reduced plasma over 24 hours in addition to crystalloid. The primary endpoint will be the total volume of all resuscitation fluids delivered between hours 0-24 postburn, in ml/kg.

Procedures: Following enrollment, patients will receive either crystalloid-based resuscitation or plasma-based resuscitation. Both groups will be started on LR according to the ISR Rule of 10s. The plasma group will receive PRP at 1 ml/Kg/TBSA/24 hours, which will not be titrated. The control group will receive additional LR at 1 ml/Kg/TBSA/24 hours. The duration of the PRP will be the first 24 hours. The Burn Navigator decision support system will be utilized to provide recommendations for the hourly titration of the LR infusion rate. The bedside team will be free to follow those recommendations or not, based on clinical judgment. The primary index of resuscitation adequacy will be an hourly urine output of 30-50 ml/hour. Arterial blood gases will be recorded every 6 hours (more frequently if clinically indicated) during resuscitation. Patients in both groups will be able to undergo rescue to include addition of additional colloid (5% albumin), high-dose vitamin C, continuous renal replacement therapy, and/or therapeutic plasma exchange, depending on local clinical practice and physician oversight. The occurrence of acute respiratory distress syndrome (ARDS), transfusion-related acute lung injury (TRALI), other organ failure (Sequential Organ Failure Assessment score), ventilator-free days, ICU-free days, 28-day and in-hospital mortality, and patient-oriented outcomes at 6 and 12 months (PROMIS-10) will be recorded. Additionally, patient blood specimens will be tested for syndecan-1 levels, pro- and anti-inflammatory cytokines, prothrombin time (PT), activated partial thromboplastin time (aPTT), coagulation factor levels, thrombin generation, and coagulation functional assessment by Rotem®.

**B2. BACKGROUND AND SIGNIFICANCE**:

Burn Shock and Resuscitation

The resuscitation of patients with extensive burns (greater than 20% of the total body surface area, or TBSA) is a significant challenge. Both over-resuscitation (too much fluid) and under-resuscitation (too little fluid) lead to potentially devastating complications (“resuscitation morbidity”), or even death. The pathophysiology of burn shock has been fairly well defined, but effective intervention strategies are mainly limited to various intravenous (i.v.) fluid regimens. The primary process which drives burn shock is a derangement of the Starling forces across the microvasculature (Shirani, Vaughan, Mason, & Pruitt, 1996). These forces include the hydrostatic pressure, the colloid oncotic pressure, and damage to the barrier function of the microvasculature.

These microvascular derangements lead to the loss of fluid, similar in composition to plasma, from the intravascular space to the extravascular space. This, in turn, causes hypovolemic shock as well as interstitial edema. Recognition of this process led to the use of plasma as a resuscitation fluid. A prominent example of the use of plasma for burn shock resuscitation followed the disaster at the Cocoanut Grove nightclub in November, 1942 (Aub, Pittman, & Brues, 1943). There, plasma was delivered by the blood bank at the Massachusetts General Hospital to the bedside diluted half and half with normal saline. During WWII, widespread availability of plasma enabled it to play a prominent role in the resuscitation of combat casualties (Kendrick, 1942), but detailed burn data from that conflict do not exist.

After WWII, various burn resuscitation formulas were developed that incorporated the patient’s burn size and weight. For example, Evans, at the first burn center established in the US, described a formula which provided 2 ml/kg/TBSA burned during the first 24 hours postburn, half of which was plasma, and the other half normal saline (Evans, 1952). Reiss et al., at the US Army Surgical Research Unit (later, the US Army Institute of Surgical Research, USAISR) and Brooke General Hospital, described the original Brooke formula. This provided 0.5 ml/kg/TBSA of plasma and 1.5 ml/kg/TBSA of normal saline (Reiss, Stirmann, Artz, Davis, & Amspacher, 1953). Although plasma was assessed as effective for burn shock resuscitation, a high rate of hepatitis transmission led to its replacement by 5% albumin in subsequent years.

These older plasma-based resuscitation formulas provide a solid starting point for the work proposed in the present proposal, now that the problem of disease transmission has been virtually eliminated by modern blood banking and plasma sterilization processes as described below.

Shift to Crystalloids

During the 1960s and 1970s a movement away from colloid for resuscitation was fueled by the concept that an extracellular sodium deficit drives the shock process in both hemorrhagic and burn shock, and that it should be corrected by vigorous administration of crystalloid fluids (Baxter & Shires, 1968; Shires et al., 1972; Shires, Coln, Carrico, & Lightfoot, 1964). Much of the subsequent focus on crystalloid resuscitation can be attributed to this theoretical basis, to include the initial 2-liter bolus prescribed by earlier versions of the Advanced Trauma Life Support program for mechanical trauma patients.

In the treatment of burn shock, a similar focus on crystalloid resuscitation resulted in the abandonment, for a time, of colloid during the first 24 hours postburn. The Parkland (or Baxter) formula called for 4 ml/kg/TBSA burned over the first 24 hours, all of it lactated Ringer’s solution (LR) (Baxter & Shires, 1968). The modified Brooke formula called for 2 ml/kg/TBSA burned during the first 24 hours, again all of it LR (Pruitt, Mason, & Moncrief, 1971). Colloid use, as 5% albumin at a dose of 0.3 to 0.5 ml/kg/TBSA, was postponed till hours 24-48 in these formulas. Pruitt and colleagues at the USAISR argued, furthermore, that the provision of varying doses of colloid (expressed as colloid-to-crystalloid ratios) during the first 24 hours postburn did not influence the rate of plasma volume loss (Pruitt & Curreri, 1971). In other words, colloid appeared to exert no volume-expanding advantage over crystalloid during the period of maximal microvascular permeability.

A single-center, randomized controlled trial of 2.5% albumin in LR vs. LR for burn shock resuscitation was subsequently published in 1983 by Goodwin et al., also from the USAISR (Goodwin, Dorethy, Lam, & Pruitt, 1983). This study demonstrated that the albumin group required a lower volume to achieve resuscitation, and experienced a faster restoration of cardiac output, than the crystalloid-only group. In this sense, Goodwin’s study contradicted Pruitt’s previous report that albumin offered no advantage over LR during the first 24 hours. The authors also measured extravascular lung water (EVLW) using the dual-indicator dilution technique, and found that the albumin group developed a higher EVLW. The clinical impact of this finding on pulmonary function or on ventilator days was not reported, and is difficult to interpret in the light of contemporaneous studies, which demonstrated no change in pulmonary microvascular permeability (Cartotto et al., 2016). The albumin group also had increased mortality, although the cause of death, and specifically any relationship to resuscitation technique, was not reported. Despite these shortcomings, this study was interpreted to mean that use of albumin should be postponed till hours 24-48 postburn.

This prescription was gradually modified by several key observations. The above studies did not precisely define the time course of postburn transvascular fluid flux. To address this question, Demling and colleagues instrumented sheep with chronic lung and soft-tissue (prefemoral) lymph fistulas (Demling, Smith, Gunther, Wandzilak, & Pederson, 1981; Harms, Bodai, Kramer, & Demling, 1982). This enabled the measurement of the lymph flow rate (an estimate of transvascular fluid flux), and of the lymph-to-colloid protein ratio (an estimate of the ability of the microvasculature to sieve plasma proteins). They found that reconstitution of microvascular barrier function in unburned tissue begins after hour 8 postburn, whereas in burned tissue it takes longer than 48 hours. These experiments supported the concept that colloids could be used as a “salvage” therapy beginning about 8 hours postburn, in those patients who appeared to be en route to an excessive fluid resuscitation volume (see below). They furthermore reinforce the rationale for using other colloids, and specifically FFP, as proposed herein.

“Fluid Creep”

Meanwhile, extensive use of the crystalloid-only formulas was accompanied by a phenomenon termed “fluid creep,” in which the volumes actually delivered sometimes greatly exceeded the formula predictions (Pruitt, 2000). In a review of the use of the modified Brooke formula at the USAISR, Cancio et al. found that patients actually received 4.9 ml/kg/TBSA (Cancio et al., 2004). Similarly, Cartotto and Zhou found that patients started on the Parkland formula received 6.3 ml/kg/TBSA (Cartotto & Zhou, 2010). There is one retrospective study comparing these two formulas. Chung et al. documented that combat casualties who were started on the modified Brooke formula received a mean of 3.8 ml/kg/TBSA; whereas those who were started on the Parkland formula received a mean of 5.9 ml/kg/TBSA. These authors concluded that “fluid begets more fluid.” A pathophysiologically-based explanation is that early provision of large volumes (as in the Parkland formula) drives a higher edema formation rate, since the microvasculature is most sensitive to hydrostatic pressure during the immediate postburn period (B.A. Pruitt, Jr., personal communication). Alternatively, more crystalloid early postburn may cause more endothelial glycocalyx damage.

Fluid creep, in term, was accompanied by increased recognition of complications (termed “resuscitation morbidity” by Dr. Steven Wolf) which ranged in severity from difficult to disastrous. Zak and colleagues showed that smaller children with larger burns, even in the absence of inhalation injury, risked edema of the airway and a need for intubation (Zak et al., 1999). Ivy et al. described abdominal compartment syndrome (ACS) in patients who received more than 250 ml/kg during the first 24 hours, a value later called the Ivy Index (Ivy et al., 2000; Ivy et al., 1999). Numerous subsequent articles have corroborated the relationship between large-volume fluid resuscitation and ACS, and have documented the high mortality of ACS in this patient population despite decompressive laparotomy (Markell et al., 2009).

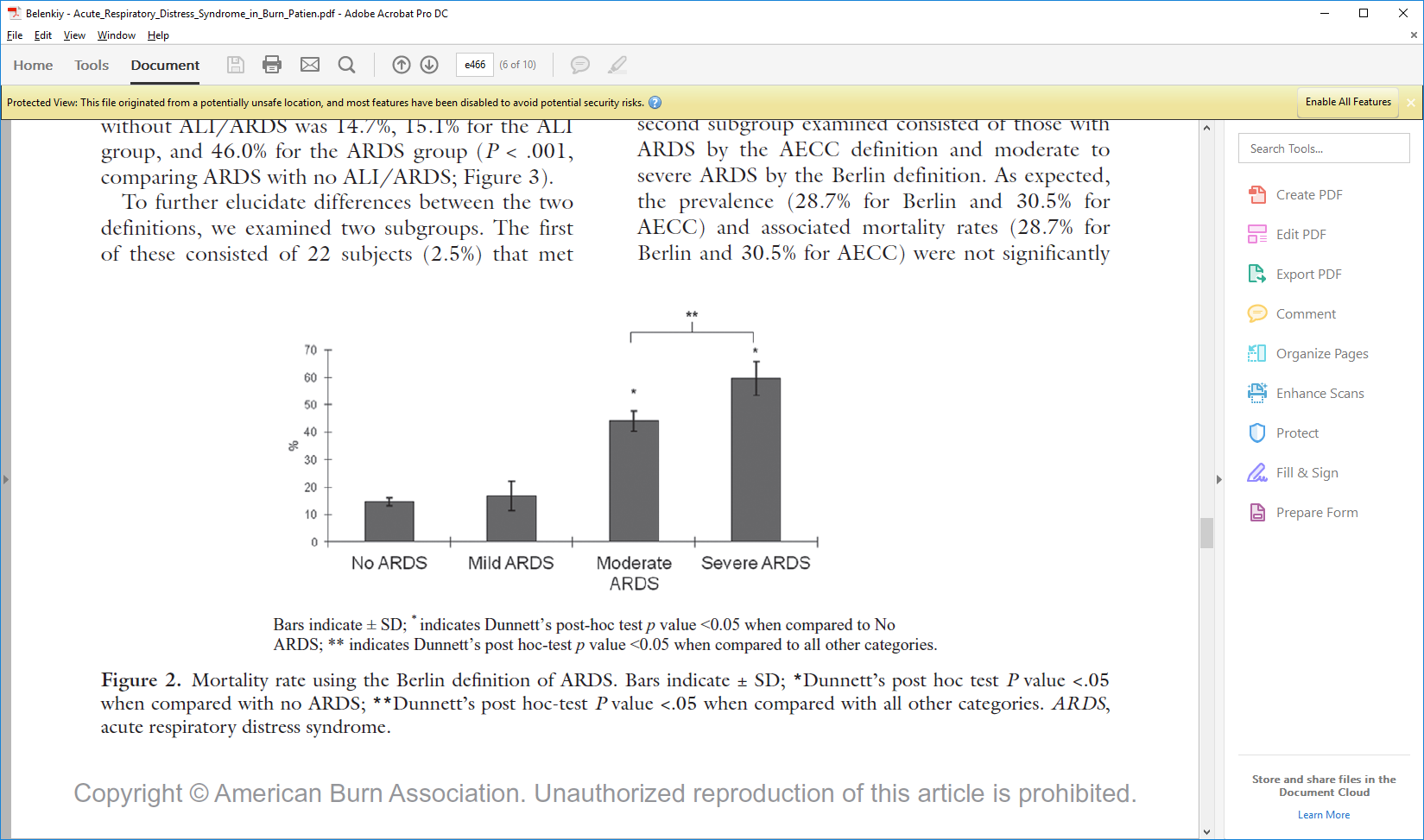
ACS is the most well-known, but not the only compartment-related consequence of over-resuscitation. Surgeons at the USAISR wrote about extremity compartment syndrome (ECS) in burn patients (Sheridan, Tompkins, McManus, & Pruitt, 1994), and identified ECS in unburned extremities following large-volume resuscitation (Beebe, Cancio, & Goodwin, 2000). Sullivan and colleagues described orbital compartment syndrome, treated with lateral canthotomy, in burn patients receiving an average of 9 ml/kg/TBSA (Sullivan et al., 2006). Insofar as timely wound healing (for example, successful skin grafting) is a *sine qua non* for survival after a major burn (Nitzschke, Aden, & Serio-Melvin, 2014), the deleterious effect of edema on wound healing (Edgar, Fish, Gomez, & Wood, 2011) is one of the strongest arguments against over-resuscitation in these patients. Indeed, Liu and colleagues recently published a predictor of open wound size which incorporates 4 variables: TBSA, fluid resuscitation volume, postburn day, and age (Liu, Cancio, Serio-Melvin, & Salinas, 2018).

Acute Respiratory Distress Syndrome (ARDS)

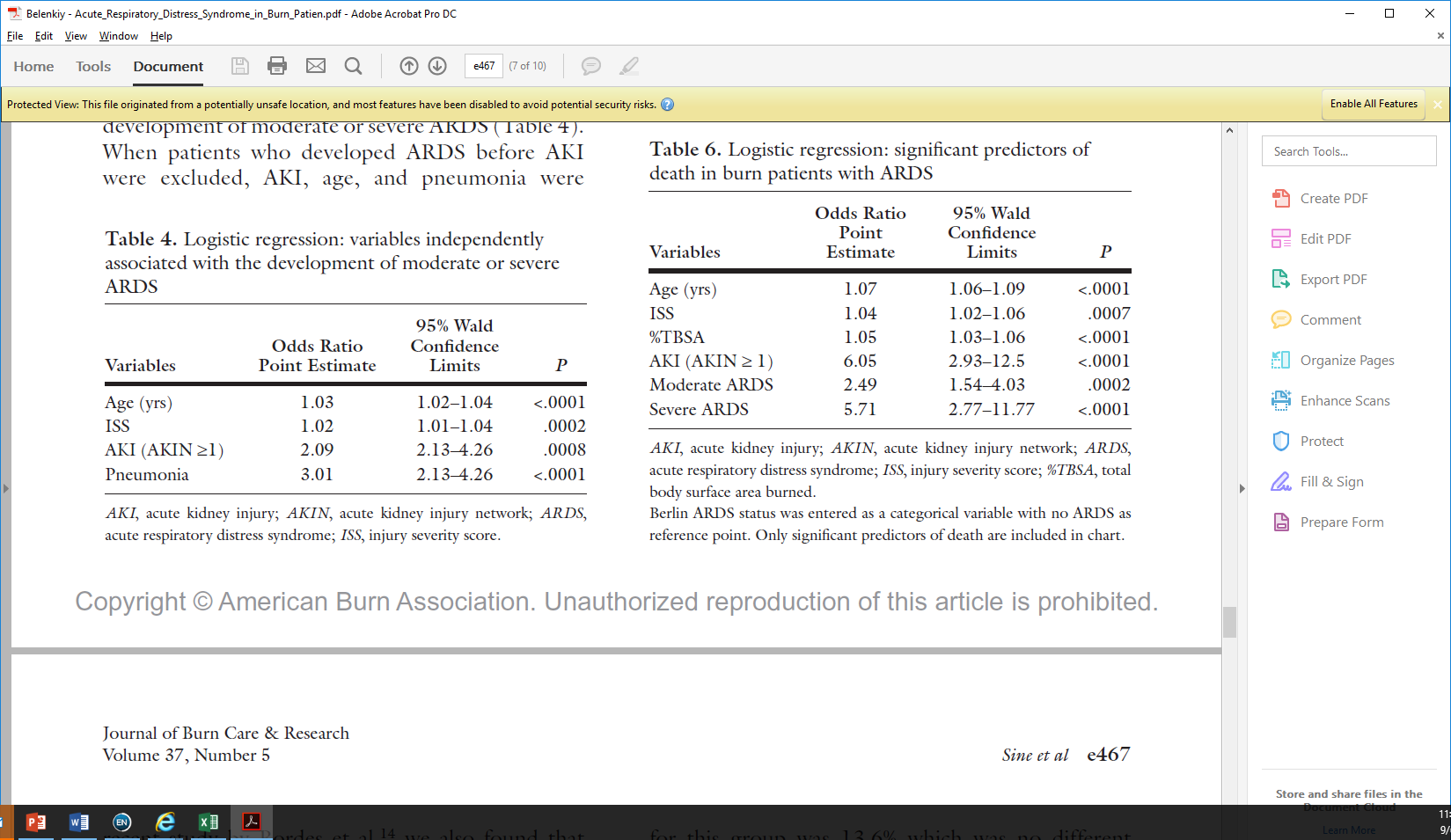
Another serious consequence of over-resuscitation is ARDS. ARDS is particularly common in critically ill burn patients. Our experience at the USAISR identified ARDS in one-third of mechanically ventilated burn patients (Sine et al., 2016). Jeschke and colleagues analyzed data from 573 burn patients from the Inflammation and Host Response to Injury (Glue Grant) study. Inclusion criteria for this study included TBSA > 20% and > 1 surgical procedure. ARDS (American-European Consensus Conference or AECC definition) was present in 20% of patients studied. Higher burn size increased risk of ARDS: the TBSA cut-off indicating increased risk (Younen’s index) was 60% TBSA for children but only 35% for adults and elderly (Jeschke et al., 2015). Though more common in patients with inhalation injury, the Salt Lake City group reported that most ARDS occurs in burn patients without inhalation injury (Hollingsed, Saffle, Barton, Craft, & Morris, 1993).

ARDS in this patient population is a highly lethal diagnosis. We compared the Berlin and AECC definitions of ARDS, finding that the former more precisely categorized ARDS mortality as shown in Figure 1 (AABB, 2016). The high mortality of moderate or severe ARDS is consistent with the prognosis of ARDS in other patient populations (Bellani, Laffey, Pham, Fan, et al., 2016). Significant predictors of moderate or severe ARDS are shown in Figure 2, and include acute kidney injury and pneumonia.

The relationship between fluid resuscitation and ARDS in burn patients has been established. Klein and colleagues reported fluid resuscitation data on 72 burn patients from the Glue Grant. The average volume received was 5.2 ml/kg/TBSA, and increased fluid volume was associated with pneumonia, bacteremia, ARDS, multiple organ failure, and death (Klein et al., 2007).



**Figure 1: Death Rate in Burn Patients with ARDS**



**Figure 2: Variables Associated with Risk of ARDS**

A larger analysis by Mason et al. of 330 Glue Grant patients was reported recently and confirmed the relationship between fluid resuscitation volume and ARDS risk. Patients were categorized by resuscitation volume into restrictive (< 4 ml/kg/TBSA), standard (4-6 ml/kg/TBSA), and excessive (> 6 ml/kg/TBSA) groups. ARDS prevalence in the restrictive group was 20%, in the standard group 35%, and in the excessive 42% (p=0.003) (S. A. Mason et al., 2016).

Non-burn ARDS data. These findings are similar to those for 1,754 adult blunt trauma patients from the Glue Grant study; the amount of crystalloid received in the first 24 hours after injury correlated with ventilator days, ICU and hospital length of stay, ARDS and multiple organ failure risk, bacteremia, and compartment syndromes—even after controlling for blood and colloid dose (Kasotakis et al., 2013). In a secondary analysis of data from the PROPPR study (in which patients were randomized by plasma:platelets:red-blood-cell-unit ratios), no difference in ARDS rates was found between the 1:1:1 and the 1:1:2 groups. However, each additional 500 ml of crystalloid given during the first 6 hours was associated with a 9% increase in ARDS risk (Robinson et al., 2018). Data on the use of plasma for resuscitation during septic shock are emerging. In a rat cecal ligation and puncture model, FFP compared to normal saline increased 48-hour survival, decreased syndecan-1, improved the post-resuscitation PaO2-to-FiO2 ratio, and reduced the lung wet-to-dry ratio (Chang et al., 2018).

In summary, ARDS is a common problem with high mortality in critically ill burn patients. Etiology is multifactorial. In many patients, it occurs in the setting of mechanical ventilation and ventilator-associated pneumonia. Thus, strategies to reduce the need for (or duration of) mechanical ventilation, are warranted. One of the ways to accomplish this is to reduce fluid resuscitation volume, thereby reducing airway and pulmonary edema, and facilitating earlier extubation. Furthermore, fluid resuscitation volume directly increases ARDS risk. Taken together, these findings indicate a need to address ARDS risk immediately upon patient admission, by employing strategies that reduce fluid resuscitation volume.

Experience with the disastrous complications caused by “fluid creep” in burn patients has led us, and others, to focus substantial efforts on preventing it. Although partially successful, more work is needed, and the present proposal is intended to do so.

Efforts to Control Burn Resuscitation

The cause of fluid creep is likely multifactorial. Lack of experience and inadequate attention to detail may play a role. This problem is more likely on the future battlefield and during prolonged field care. We and others have observed that clinicians appear more apt to increase the fluid infusion rate during periods of oliguria, than they are to decrease it during periods of excessive urine output (Cancio et al., 2005; Cartotto & Zhou, 2010). Sullivan and coauthors noted an increase in the use of opioid analgesics between the late 1970s and the early 2000s, which they termed “opioid creep” (Sullivan et al., 2004). The effect of more opioid use during burn shock is to increase the likelihood of hemodynamic instability and thus fluid resuscitation requirements, a relationship confirmed by Wibbenmeyer et al. (Wibbenmeyer et al., 2010). Possibly, changes in the medical fitness of the population, with an increased incidence of diabetes and of substance addiction, may also affect fluid resuscitation needs in these groups (Engrav et al., 2000).

To control fluid creep and preclude over-resuscitation, we developed a computerized decision support program, Burn Navigator (Salinas et al., 2011). This program uses the linear trend in urine output (UO) from the last 3 hours, as well as data such as the burn size and hour postburn, to predict the next hour’s UO. It then recommends an infusion rate adjustment that would achieve a UO within the target range of 30-50 ml/hr. Use of this decision support algorithm at the USAISR burn center was associated with a decrease in fluid resuscitation volumes, in ventilator-free days, and in mortality. At the time of this writing, a multicenter prospective observational evaluation of Burn Navigator is underway.

Pharmacological approaches to reducing fluid needs have been few. A single-center randomized controlled trial of high-dose ascorbic acid (66 mg/kg/hr) by Tanaka et al. in Tokyo demonstrated a fluid-sparing effect (Tanaka et al., 2000). A subsequent multicenter trial in the US failed to materialize because an investigational new drug (IND) application was mandated, but adequate funding for this generic drug was unavailable (NCT00350077 at clinicaltrials.gov). Still, some clinicians use high-dose ascorbic acid in patients who appear to be failing conventional resuscitation, whereas others use it routinely in the care of patients with large burns (Kahn, Beers, & Lentz, 2011). Because this therapy targets a known mechanism for burn shock--oxidative stress--it seems that it could play a role (Dubick, Williams, Elgjo, & Kramer, 2005). But the true impact remains to be confirmed, and there is concern that osmotic diuresis, rather than an antioxidant effect, may explain the findings.

Burn shock is also mediated in part by the elaboration and release of circulating inflammatory mediators, such as cytokines and chemokines. This concept provides support for the use of “blood purification” techniques such as continuous renal replacement therapy (CRRT) by means of veno-venous hemofiltration (CVVHF), or therapeutic plasma exchange (TPE) (Linden, Stewart, & Kreyer, 2014). At the USAISR burn center, CRRT is often initiated during the burn shock period for the patient with acute renal failure, unacceptable metabolic acidosis, hyperkalemia, and/or elevated fluid requirements, which portend a risk of exceeding the Ivy Index of 250 ml/kg. This could be viewed as an extension of experience published by Chung et al. with the treatment of Acute Kidney Injury Network (AKIN) level 3 renal injury or AKIN level 2 with shock, in septic burn patients (Chung et al., 2008; Chung, Lundy, & Matson, 2009). However, evidence of efficacy in the initial burn shock setting does not exist.

Others have used TPE during the difficult resuscitation. Klein et al. at the Harborview burn center reviewed 37 patients who received this modality over a 5-year period (2001-5) (Klein et al., 2009). Their use of TPE was not protocolized but generally occurred if the patient required twice the Parkland rate. TPE resulted in a decrease in hourly fluid volume and in improvements in UO, base deficit, lactate, and hematocrit levels. Neff and colleagues at Winston-Salem reported use of TPE in 40 burn patients over a two-year period (Neff, Allman, & Holmes, 2010). Their more aggressive criteria for TPE included ongoing need for more than 1.2 times the predicted fluid resuscitation rate, which was based on a 3 ml/kg/TBSA formula. Fresh frozen plasma (FFP) was used for TPE for most of Neff’s patients. TPE was associated with similar improvements in fluid input, mean arterial pressure (MAP), UO, and lactate. There are no controlled clinical trials.

The most common intervention for the fluid resuscitation gone awry is the institution of 5% albumin before the 24th postburn hour. Several algorithms have been proposed to determine when to do this. In the mid-1990s, Cancio and Pruitt recommended calculating the projected 24-hour fluid resuscitation volume at postburn hour 12. If this volume is predicted to exceed 6 ml/kg/TBSA, they called for institution of 5% albumin before hour 24 (at the dose usually used for the second day) (Cancio, Mozingo, & Pruitt, 1997). Salinas found that early albumin, used in this fashion, was associated with a reduction in infusion rates 3 hours later (Cancio, Salinas, & Kramer, 2016). At the University of Michigan, Park et al. described a similar protocol. This was associated with a decrease in vasopressors, ventilator days, and mortality, although a difference in fluid volumes was not significant (S. H. Park, Hemmila, & Wahl, 2012).

The most well-known protocol for “albumin rescue” was described by Saffle and colleagues. In that algorithm, resuscitation is started at the Parkland rate. The main trigger for initiating albumin is an hourly crystalloid rate, which is twice the calculated rate, for 2 hours (Saffle, 2007). A review of this approach at the University of Utah showed that albumin patients were sicker (higher prevalence of inhalation injury, higher initial lactate, longer time to completion of resuscitation) and actually received more fluid than those who did not require “rescue”; however, there was no difference in mortality. In fact, albumin appeared to be protective in a logistic regression model of mortality risk. Furthermore, in a model that considered albumin, resuscitation volume, and inhalation injury, only the latter was predictive of ARDS risk (Cochran, Edelman, Saffle, & Morris, 2007). Dulhunty and coauthors from Brisbane studied 80 patients with TBSA > 15%. Higher fluid resuscitation volume was associated with pneumonia and with extremity compartment syndrome (see below), whereas colloid use (type of colloid not specified) during the first 24 hours reduced compartment syndrome risk (Dulhunty, Boots, Rudd, Muller, & Lipman, 2008).

Consistent with the above findings, in 2009 Greenhalgh published the results of an International Society for Burn Injuries (ISBI)/American Burn Association (ABA) survey of burn resuscitation practice which, while mentioning the Parkland formula as the preferred formula and LR as the preferred solution, approach, also point to the initiation of colloid during the first 24 hours by 49.5% of respondents (Greenhalgh, 2010). Another international survey of burn resuscitation practice, carried out by the European Society of Intensive Care Medicine (ESCIM) Burn ICU Working Group, was just published. The indications for colloid use identified by the respondents were, in order of prevalence: high crystalloid volume requirement; persistent hypotension; low plasma albumin level; decreased UO; fixed TBSA (e.g. > 30%); ARDS; systematically 6-8 h after injury; and inhalation injury (Soussi et al., 2018). A prospective multicenter observational study of resuscitation, to include albumin use, is currently ongoing (Acute Burn Resuscitation Multicenter Prospective Observational Trial, or “ABRUPT”, NCT03144427 at clinicaltrials.gov). A randomized controlled trial of albumin rescue has not been performed.

The above experience demonstrates that a fundamental shift in burn resuscitation towards earlier use of colloids has been underway for years, ever since the first description of “fluid creep” and the complications, including respiratory failure, which follow such over-resuscitation. However, there is no consensus on this topic, and clinical equipoise exists regarding the early use of colloids for resuscitation. We will now turn our attention to the important role played by the endothelium in shock states, and to efforts to direct resuscitation strategy at preserving it.

Endotheliopathy of Trauma

Meanwhile, a comprehensive reevaluation of fluid resuscitation strategy in trauma patients has occurred over the last decade, energized by experience with combat casualties from the wars in Iraq and Afghanistan (Holcomb et al., 2007). This effort began with “hemostatic resuscitation”, which incorporates plasma, platelets, and red blood cells in 1:1:1 ratios into the initial management of seriously injured patients (Holcomb et al., 2015). A further development addressed the process whereby trauma patients become coagulopathic (“coagulopathy of trauma”), and the role of the endothelium in this process (“endotheliopathy of trauma”) (Ostrowski et al., 2017). This work has not only changed our approach to the initial care of the exsanguinating patient, but also has expanded our understanding of the role of the microvasculature in the response to other injuries such as burns.

Damage to the glycocalyx is the key to the endotheliopathy of trauma. The glycocalyx is composed of a three-dimensional meshwork of proteoglycans and glycoproteins. The proteoglycans consist of a protein core (syndecans, glypicans, others), to which glycosaminoglycans (heparan sulfate, hyaluronic acid, others) are attached. The glycoproteins act as adhesion molecules and include E and P selectins, integrins, and immunoglobulins, which participate in hemostasis and inflammation (Alphonsus & Rodseth, 2014).

The glycocalyx not only forms a passive barrier between the blood and the endothelium, but also actively mediates the relationship between the 2 tissues. The glycocalyx is essential for maintaining an anticoagulant surface on the endothelium (Chappell et al., 2014). The glycocalyx “contains” a large volume (1-1.7 liters) of non-circulating plasma within its meshwork (Schott, Solomon, Fries, & Bentzer, 2016). It also serves as a “sensor,” whereby information about fluid mechanical shear stress is transduced to the endothelial cell (Pahakis, Kosky, Dull, & Tarbell, 2007). Most importantly, the net negative charge of the glycocalyx, imparted by glycosaminoglycan side chains, enhances the endothelium’s ability to repel blood cells and platelets, and to sieve molecules larger than 70 kDa (Alphonsus & Rodseth, 2014).

Shedding of the glycocalyx may occur in response to ischemia/reperfusion, hypoxia, oxidative stress, hyperglycemia, hypervolemia, catecholamines, hemorrhagic shock, cardiac arrest, and sepsis (Alphonsus & Rodseth, 2014; Barelli & Alberio, 2018; Grundmann et al., 2012; Haywood-Watson et al., 2011; Ostrowski et al., 2015; Rehm et al., 2007). Enzymes called “sheddases” mediate the degradation of the glycocalyx, to include matrix metalloproteinases, heparanases, hyaluronidases, and proteases (Barelli & Alberio, 2018). Compounds which reportedly protect the glycocalyx have been reviewed (Schott et al., 2016) and include hydrocortisone, antithrombin III, protein C, nitric oxide, hyaluronic acid, chondroitin sulfate, sulodexide (a heparin and dermatan sulfate mixture), lidoflazine (a calcium-channel blocker), albumin, hydroxyethyl starch, N-acetylcysteine, and metformin. Clinically, this is associated with shedding of the syndecan-1 ectodomain. Shed ectodomains following trauma are associated with enhanced shock, inflammation, and endothelial damage (Chignalia et al., 2016), and independently predict mortality in injured patients (Johansson, Stensballe, Rasmussen, & Ostrowski, 2011).

A substantial body of microvascular physiology research supports the concept that choice of perfusate influences microvascular permeability, and that this permeability is mediated by the glycocalyx; see our recent review (Gurney, Kozar, & Cancio, 2019). These studies provide evidence in support of the superiority of plasma to albumin or to crystalloid solutions for glycocalyx protection.

Accordingly, investigators have examined the role of the glycocalyx in animal models of hemorrhage. Kozar et al. conducted studies of rats with hemorrhagic shock, then resuscitated with either LR or plasma. Shock caused degradation of glycocalyx by electron microscopy. The glycocalyx was partially restored by plasma, but not by LR, and pulmonary syndecan-1 mRNA expression was higher in animals treated with plasma than with LR. Plasma mitigated lung injury as well (Kozar et al., 2011). Nelson and colleagues resuscitated rats bled 30% with FFP, albumin, or Ringer’s acetate. Both FFP and albumin restored plasma volume, whereas Ringer’s acetate did not. Heparan sulfate levels were lower in the FFP and albumin groups. Syndecan-1 levels did not differ among groups (Nelson, Statkevicius, Schott, Johansson, & Bentzer, 2016).

Torres Filho and colleagues evaluated various resuscitation fluids in rats with 40% blood volume hemorrhage. Intravital microscopy was used to measure glycocalyx thickness in cremasteric postcapillary venules. Glycocalyx thickness (negatively), and microvascular permeability (positively), were correlated with plasma syndecan-1 and heparin sulfate levels. Overall, resuscitation with crystalloid solutions (LR or normal saline) evoked glycocalyx damage and increased permeability, resuscitation with fresh whole blood or plasma elicited protection, and albumin had an intermediate effect (Torres Filho, Torres, Salgado, & Dubick, 2016).

Pati and colleagues evaluated albumin, FFP, and the factor concentrate, Kcentra, in a mouse model of hemorrhagic-shock-induced pulmonary vascular leak. Interestingly, Kcentra and FFP, but not albumin, inhibited vascular permeability in the model. Kcentra was found to contain nearly 100 proteins, to include albumin, prothrombin, factors VII, IX, and X, proteins C and S, and antithrombin III. As in the case of FFP, the proteins in Kcentra responsible for the observed effects remain uncertain (Pati et al., 2016).

In clinical studies, restoration of the glycocalyx is increasingly recognized as an important therapeutic goal. Holcomb and colleagues have demonstrated a decrease in mortality and improved outcomes *in vitro*, *in vivo*, and clinically after trauma and hemorrhagic shock from plasma-based resuscitative strategies (Holcomb et al., 2015; Holcomb, Fox, Wade, & Group, 2013). These benefits appear to extend beyond the ability to correct trauma-induced coagulopathy and provide hemorrhage control, and involve protective effects to a dysfunctional endothelium (Peng et al., 2013). Early plasma-based resuscitation reverses the endotheliopathy of trauma by restoring the glycocalyx. Using plasma as the primary volume expander rather than crystalloids has been associated with decreased morbidity and mortality in hemorrhagic shock patients (Cotton et al., 2011). Joseph et al. found in trauma laparotomy patients that minimizing the use of crystalloids was associated not only with improved outcomes but also virtually eliminated ACS (Joseph et al., 2014). In a multi-institutional analysis of bleeding patients requiring massive transfusion who were resuscitated with modern-day high plasma ratios, the increased use of crystalloids was still associated with increased morbidity (Duchesne et al., 2013).

In brief, extensive studies in animal models and trauma patients indicate the importance of the endothelial glycocalyx, to include in the lungs (Peng et al., 2013), and the potential superiority of plasma to other fluids in protecting or restoring it following trauma/hemorrhage. We will now present the central hypothesis of the present proposal, which is that the same problem of glycocalyx injury also pertains to burn shock and can be addressed with plasma-based resuscitation.

Endotheliopathy of Burns

We propose that, similarly, there is an endotheliopathy of burns that will be abrogated by a paradigm shift in burn resuscitation away from a crystalloid-based strategy to a plasma-based strategy. There is recent evidence that syndecan-1 shedding also occurs following burns. Cruz et al. in a rat model of 25% and 40% TBSA burns demonstrated increased syndecan-1 shedding proportional to burn size (Cruz, Carney, Chen, Moffatt, & Shupp, 2017). In a prospective observational clinical study, and after adjusting for age, sex, TBSA, and inhalation injury, Osuka et al. found that syndecan-1 shedding was independently correlated with increased fluid resuscitation volume and the development of burn-induced compartment syndromes (Osuka et al., 2018).

A significant knowledge gap exists concerning the utility of plasma in burn resuscitation in the modern era, but the available data suggest that it may be the fluid of choice. Du et al. from Pittsburgh compared LR, FFP, and hypertonic saline (HTS) for burn resuscitation (Du, Slater, & Goldfarb, 1991). The volume infused was a mean of 4.8 ml/kg/TBSA in the LR group, 3.16 in the HTS group and 2.68 in the FFP group. The median % weight gain at the end of the first day of treatment was 10.7 in the LR group, 7.9 in the HTS group and 2.4 in the FFP group. Their formula incorporating FFP for resuscitation is called the Slater formula (Cartotto et al., 2016).

O’Mara and colleagues from the same group conducted a single-center randomized controlled trial of FFP (plus 2000 ml of LR) vs. LR (at the Parkland dose) (O'Mara, Slater, Goldfarb, & Caushaj, 2005). The FFP group demonstrated lower volume needs than the LR group (0.21 vs. 0.26 ml/kg) and virtually eliminated intra- abdominal hypertension. Plasma has become the mainstay of burn resuscitation for some burn centers; the above-mentioned ISBI/ABA survey stated that FFP was the preferred fluid for 13.9% of respondents (Greenhalgh, 2010). These data suggest that there is growing acceptance in the burn community concerning the choice of plasma vs. LR for early burn shock resuscitation.

Transfusion-Related Acute Lung Injury

A discussion of plasma would be incomplete without consideration of transfusion-related acute lung injury (TRALI). The pathophysiology of TRALI is hypothesized to involve the transfer of donor antileukocyte antibodies and/or biologically active lipids, which initiate an inflammatory response and alveolar-capillary membrane injury. However, alternative explanations include the cellular components of older units of stored blood. Analysis is difficult because many patients have other predisposing factors for lung injury (El Kenz & Van der Linden, 2014; Toy et al., 2005). In a prospective observational trial at 2 centers, there were 463,207 units of blood or products transfused, and 89 TRALI cases. The incidence of TRALI was 0.87 to 2.57 per 10,000 units. Risk factors included transfusion of female donor plasma, volume of HLA Class II antibody (NBG > 27.5), and volume of anti-human neutrophil antigen (Toy et al., 2012). In contrast to TRALI, the entity “possible TRALI” (pTRALI) has been defined as new ALI within 6 hours of transfusion, with a clear temporal relationship to an alternate risk factor for ALI. When such pTRALI conditions exist, evidence points away from transfusion, and towards pre-existing patient-related risk factors to include chronic alcohol abuse, smoking, shock, and a positive fluid balance (Toy et al., 2015).

Several papers have aimed to identify risk factors for TRALI following injury. We conducted a prospective observational study of patients admitted to the ICU at the Combat Support Hospital in Baghdad, Iraq during 2008 who required >5 units of blood during the first 24 hours after injury. Twenty-two of 87 subjects (33%) developed acute lung injury (ALI). Those who did, had a higher ISS, and received more FFP (22 vs. 12), more packed red blood cells (22 vs. 13), and more platelets (5 vs. 1). Logistic regression retained FFP dose and presence of direct pulmonary injury as predictors of ALI. Long-term follow up data were not available, and thus the relationship between ALI and mortality could not be determined (Edens et al., 2010). A paper by the Inflammation and Host Response to Injury (Glue Grant) investigators evaluated patients with blunt injury and > 8 units of packed red blood cells during the first 12 hours. Patients who received a ratio of FFP to packed red blood cells > 1:1.5 required less blood and had lower mortality at 24 hours. Cox regression showed that FFP independently correlated with a 52% lower risk of mortality. There was also an increased risk of ARDS, but not of nosocomial infection or of multiple organ failure (Sperry et al., 2008). A follow-on paper by the same group used all those patients with blunt injury who received a transfusion who lived past 48 hours. In this data set, FFP was not associated with overall mortality or nosocomial infection, but with an increased risk of multiple organ failure and ARDS. When early deaths (first 48 hours) were included in the analysis, FFP led to a decreased risk of mortality (Watson et al., 2009).

In brief, these studies in indicate that FFP, as a component of hemostatic resuscitation, is lifesaving in the patient with hemorrhagic shock; and that--given the mortality benefit--it has a known but acceptable risk of TRALI. In this protocol, we will assess the mortality benefit together with hemostatic benefit of plasma resuscitation, including its effects on clotting initiation, clotting speed, clot strength and fibrinolysis.

Pathogen-Reduced Plasma via the INTERCEPT System

The previously mentioned studies using FFP in burn patients were isolated reports, and despite their promising results, crystalloid resuscitation remains the standard of care for burn resuscitation. Enthusiasm for plasma was constrained by the risk of transfusion-transmitted infection; this will be abrogated by the use of pathogen-reduced plasma as proposed in the current application. There are two FDA-licensed plasma products prepared with pathogen-reduction treatment (PRT) available in the US: INTERCEPT Plasma (Cerus Corporation) and Octaplas (Octapharma). These products are intended to reduce the risk of transfusion-transmitted infection (TTI) in platelet and plasma components. INTERCEPT plasma is treated with amotosalen and UVA light and inactivates a broad spectrum of bacteria, viruses (including enveloped viruses and some non-enveloped viruses), protozoa, and leukocytes. In contrast to Octaplas, INTERCEPT plasma uses single-donor and small-batch whole-blood-donor pools, is manufactured in non-DEHP containers, retains sufficient levels of pro-coagulant and anti-thrombotic proteins, and has been extensively evaluated in proteomic studies, pre-marketing, and post-marketing clinical studies including studies of liver transplant and therapeutic plasma exchange. After thawing, INTERCEPT plasma can be re-labeled as thawed plasma and stored for up to 5 days at 4oC. On the basis of these characteristics, INTERCEPT plasma has a better inactivation and therapeutic profile plus better operational logistics for ease of use and reduced wastage.

In vivo prospective studies of the INTERCEPT concept were originally performed in chimpanzees. Animals were protected by INTERCEPT for hepatitis B (HBV) and hepatitis C (HCV) after receiving full unit doses with follow up for 6 months, whereas untreated (conventional) blood products caused hepatitis (HJ Alter et al., 1988). There are human case reports and epidemiologic studies concerning the superior safety profile of the INTERCEPT-treated products. Candotti and colleagues (D Candotti et al., 2019) showed that INTERCEPT protected patients exposed to blood products contaminated with occult HBV, while patients who received conventional (non-PRT) blood products from these donors were infected with HBV. Transfusion-transmitted bacterial infection (TTBI) studies from France and Switzerland demonstrated a statistically significant reduction in risk of TTBI when INTERCEPT was used (L Corash and Benjamin RF, 2016). Similar findings were reported in massive datasets from France, Switzerland, and Belgium, comparing delayed large-volume bacterial culture (DLVBC) and INTERCEPT (RJ Benjamin, Braschler, Weingand, & Corash, 2017).

Conclusions

In conclusion, we plan a prospective, randomized, controlled, multicenter trial of Pathogen-Reduced Plasma vs. a standard-of-care therapy based on lactated Ringer’s solution, for the resuscitation of patients with acute burns > 20% of the total body surface area. Use of plasma for resuscitation is founded, in part, on multiple studies of both plasma and albumin which demonstrate the benefits of colloid-based resuscitation in reducing total resuscitation volume and the risk of resuscitation morbidity. Furthermore, use of plasma instead of albumin is predicated on the former’s demonstrated ability to protect the endothelial glycocalyx in a variety of shock models, to include burns. The benefits of reduced resuscitation volume include a reduction in the risk of ARDS, a common and frequently lethal complication in burn patients, as well as several other serious complications of over-resuscitation.

**B3.** **MILITARY RELEVANCE:** Thermal injury has occurred in 10% of the casualties on the current battlefields, reflecting the leading role of improvised explosive devices (IEDs) and subsequent fires as an injury mechanism. Resuscitation of these casualties is labor- and supply-intensive, often requiring 20 or more liters of crystalloid solution during the first 24 hours--thus imposing significant logistical burden on deployed medical treatment facilities. Experience during the current wars demonstrated a high prevalence of life-threatening complications secondary to over-resuscitation, such as ACS, ECS, and ARDS. Thus, strategies that reduce fluid resuscitation volumes will increase post-burn survival in this high-risk population. Finally, we anticipate that plasma and its byproducts will increasingly be available on the future battlefield for the resuscitation of casualties with hemorrhagic shock and will likely replace crystalloid solution for far-forward use. The utility of PR plasma in the resuscitation of thermally injured patients thus must be fully defined.

**B4. OBJECTIVES/SPECIFIC AIMS/RESEARCH QUESTIONS**

Hypotheses: Administration of plasma for resuscitation after burn injury will 1) reduce 24-hour and 48-hour resuscitation volumes and 2) reduce the incidence of acute respiratory distress syndrome, multi-organ failure and other resuscitation-related morbidities.

Objectives:

* Specific aim 1: To determine whether administration of Pathogen-Reduced Plasma during burn resuscitation results in decreased total resuscitation volumes compared to standard-of-care crystalloid-based resuscitation.
* Specific Aim 2: To determine whether Pathogen-Reduced Plasma administration during burn resuscitation reduces ARDS.
* Specific Aim 3: To determine the effect of Pathogen-Reduced Plasma administration on the endotheliopathy, inflammation and coagulation of burns.

**B5**. **RESEARCH PLAN**

**B5.1 Research Design** This is an open-label, phase IV, multicenter, randomized controlled prospective clinical trial in patients with burns. The study model is parallel (between-patient). The intervention to be tested is Pathogen-Reduced Plasma for burn shock resuscitation vs. standard-of-care resuscitation.

**Endpoints**:

* Primary endpoint: The total volume of all resuscitation fluids delivered between hours 0-24 postburn, in ml/kg.

Secondary endpoints:

*Specific Aim 1 (Resuscitation Volumes):*

* The total volume of all resuscitation fluids delivered between **hours 0-48** postburn, in **ml/kg**
* The total volume of all resuscitation fluids delivered between **hours 0-24** and **0-48** postburn, in **ml/kg/TBSA**
* Severity and duration of hemodynamic instability during hours 0-48 postburn (norepinephrine equivalents)
* Severity and duration of metabolic acidosis during hours 0-48 postburn (arterial lactate levels)
* Incidence of “rescue,” defined as any of the following:
  + Initiation of extracorporeal therapy, i.e. continuous renal replacement therapy or therapeutic plasma exchange, during the first 48 hours postburn
  + Infusion of high-dose ascorbic acid (66 mg/kg/hr) during the first 48 hours postburn
  + Initiation of a continuous infusion of albumin before hour 24 postburn

*Specific Aim 2 (ARDS):*

* Incidence and severity of ARDS using Berlin criteria
* Duration of mechanical ventilation in survivors
* Ventilator-free days in the first 30 days
* Multi-organ failure (Sequential Organ Failure Assessment scores)
* Length of ICU and hospital stays
* In-hospital mortality
* Patient-reported outcomes 6 months after injury
* Incidence of transfusion-related acute lung injury (TRALI; consensus definition)
* Incidence of venous thrombo-embolic events

*Specific Aim 3 (Endotheliopathy of Burns):*

* Syndecan-1 levels
* Cytokines IL-6, TNFα, IL-1β, and IL-10
* Rotational thromboelastometry (Rotem®), PT, aPTT, and coagulation factor levels
* Thrombin generation

**B5.2 Research Subjects/Population(s)**

**B5.2.1**  **Subject Population(s)**

Adult male and female patients (age ≥ 18 years and < 65 years) admitted to an American Burn Association-verified burn center within 8 hours of sustaining a burn injury of > 20% total body surface area and undergoing intravenous fluid resuscitation (projected to continue for at least 24 hours), guided with the Burn Navigator.

**B5.2.2 Number of Subjects, Records, and/or Specimens**

Using an anticipated average fluid resuscitation with the Burn Navigator of 4.2 ml/kg/TBSA and an anticipated goal of 3.0 ml/kg/TBSA, we performed a power analysis with α=0.05 and β = 90% and determined that we require 47 subjects per treatment group (94 subjects total). Each of the 6 participating centers will enroll approximately 16 subjects over 2 years (see Table, below).

## Table: Anticipated Enrollment by Sites

|  |  |
| --- | --- |
| *Site* | *Enrollment* |
| University of Washington Medicine Regional Burn Center, Seattle, WA | 16 |
| The Vanderbilt Burn Center, Nashville, TN | 16 |
| University of Alabama at Birmingham Burn Center | 16 |
| U.S. Army Burn Center, Fort Sam Houston, TX | 16 |
| University of Texas Medical Branch | 16 |
| University of Texas Southwestern | 16 |

If accrual at one or more sites is lower than anticipated, the other sites will be encouraged to enroll additional subjects to meet the overall study recruitment milestones (with appropriate modification of their IRB and HRPO approvals).

B5.2.3 Inclusion Criteria

* Age > 18 years
* Weight > 40 kg
* Thermal injury size ≥ 20% TBSA
* Admitted to the burn center and enrollable within 8 hours of injury
* Expected to receive intravenous resuscitation fluids for at least 24 hours after injury
* Expected to live > 24 hours after injury

B5.2.4 Exclusion Criteria

* Chemical injury
* Deep electric injury resulting in clinically evident myoglobinuria.
* Associated non-thermal injuries (defined as: a requirement [because of traumatic injury] for blood transfusion, major intracavitary surgery (craniotomy, thoracotomy, laparotomy), angioembolization, or endovascular surgery during the first 24 hours after injury
* Inability to obtain informed consent
* Decision not to treat due to injury severity or other factors
* Patient age > 65 years or < 18 years
* Presence of anoxic brain injury that is not expected to result in complete recovery
* Patient already receiving plasma infusion, or judged to be likely to require plasma infusion
* Patient already receiving “rescue procedures” (albumin infusion, CRRT, TPE, or high-dose ascorbic acid)
* Existence of pre-morbid conditions:
* Congestive heart failure (NYHA Class IV)
* End-stage kidney disease (dialysis patient)
* Cirrhosis of the liver
* Oxygen-dependent chronic obstructive pulmonary disease
* Malignancy currently under treatment
* Previous bilateral lower extremity amputations

**B5.3 Research Procedures**

**Timing and procedures**: Patients will be consented and enrolled within 8 hours of burn injury. Blood specimens will be drawn at admission and at 12, 24, and 48 hours postburn. These blood specimens will be spun and the plasma will be sent to the ISR for further processing. At the ISR, the Blood Coagulation Research Division will perform measurements of PT, aPTT, Rotem® and coagulation factor levels. ISR will send plasma to the University of Maryland for measurement of pro- and anti-inflammatory cytokines (including IL-6, TNFα, IL-1β, IL-10, IL-8 and GMCSF), and of syndecan-1 as an indicator of the endotheliopathy of burns. ISR will also send plasma to Cerus Corporation (Concord, CA) for thrombin-generation testing. Fluid resuscitation procedures are described below in Arms/Study Groups and in the Table.

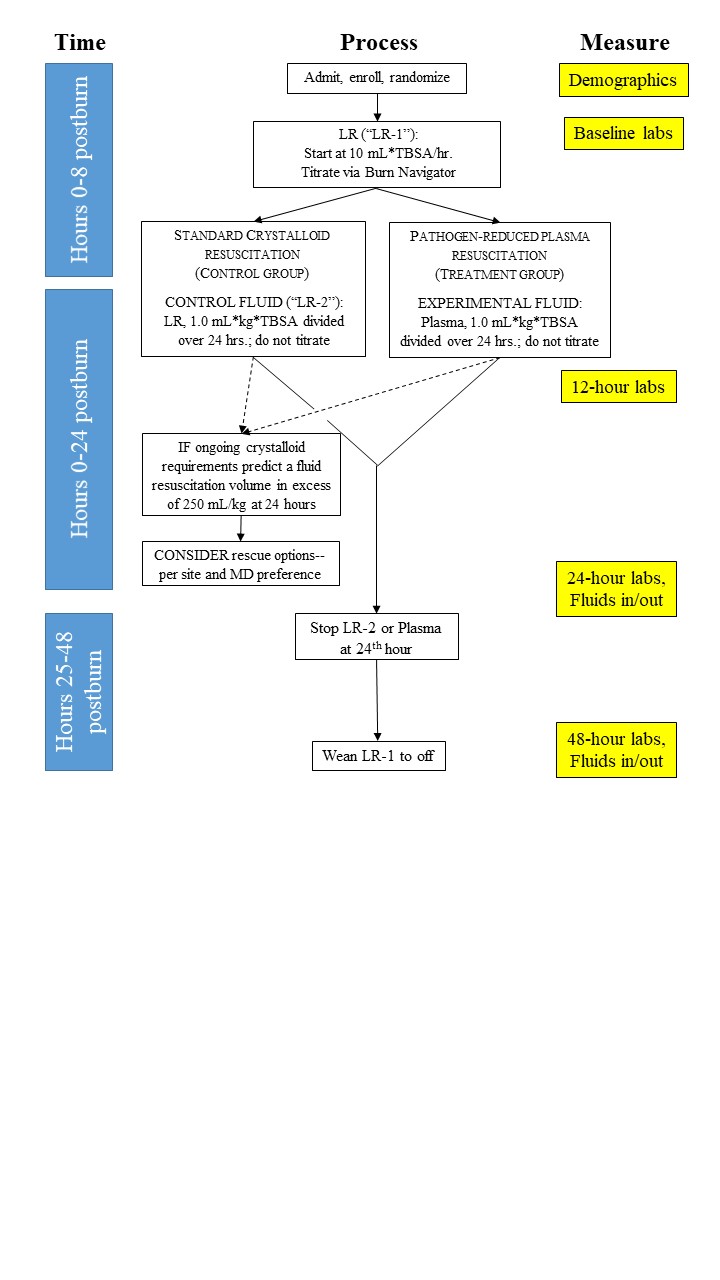
In addition, upon the completion of plasma infusion in the treatment group, 10 ml of plasma will be collected from the infusion bags used in each patient and stored at -80°C. These samples will be sent to the ISR for the same measurements as those from patient plasma samples.

**Arm/Study Groups:** see Figure, below.

* **Both the Treatment and the Control Groups** will receive an infusion of LR (“**LR-1**”) according to the ISR Rule of Tens.This formula estimates the initial fluid requirements as 10\*TBSA, in mL/hr. For example, a patient with a 50% TBSA burn would receive an initial rate of LR at 10\*50=500 mL/hr. This formula yields results which are close to those of the modified Brooke formula. (Chung et al., 2010) In both groups, this infusion will be titrated according to the recommendations of the Burn Navigator decision support system. It will be continued till the end of the 48th postburn hour, or until the clinician determines that it is no longer needed.
* **Titration of LR-1 infusion:** This will be done hourly using the Burn Navigator system for decision support. Burn Navigator is an FDA-approved, commercial off-the-shelf system (Arcos Medical, Houston, TX). It is used during burn shock resuscitation at each of the 5 participating burn centers in this study. The logic employed by the system is described above. It is used as an aid to resuscitation, rather than as a closed-loop control system; that is, the physician is free to accept or modify the recommendations of the system based on clinical judgment. (Salinas et al., 2011.) Burn Navigator will be used to titrate the LR-1 infusion only, but will be used to record the other infusions.
* **Control Group:** This group will receive an additional infusion of LR (“**LR-2**”) based on the formula: hourly rate, mL/hr = (1 mL\*kg\*TBSA)/24 hr. For example, a 70-kg patient with a 50% burn would receive 146 mL/hr of LR (in addition to LR-1). This infusion will not be titrated. It will be discontinued at the end of the 24th postburn hour.
* **Treatment Group:** This group will receive an additional infusion of Pathogen-Reduced **Plasma** based on the formula, hourly rate, mL/hr = (1 mL\*kg\*TBSA)/24 hr. For example, a 70-kg patient with a 50% burn would receive 146 mL/hr of Plasma (in addition to LR-1). This infusion will not be titrated. It will be discontinued at the end of the 24th postburn hour.
* **Albumin rescue (AR) procedure:** AR is defined as a continuous infusion of albumin before the 24th postburn hour. In this study, AR will not be permitted any earlier than the 10th postburn hour. The decision to perform AR will be based primarily on a high projected fluid infusion volume, as calculated by Burn Navigator. (Burn Navigator provides situational awareness on projected fluid volumes; that is, starting at postburn hour 10, it calculates a 24-hour volume projection. It alarms ‘orange’ if that volume is > 200 ml/kg, and it alarms ‘red’ if that volume is > 250 ml/kg.) The decision to do AR will be at the discretion of the clinician. The AR dose, if used, will be adopted from the modified Brooke formula for the second 24 hours postburn: hourly rate, mL/hr = (0.5 mL\*kg\*TBSA)/24 hr. This infusion will be given in addition to the aforementioned infusions, and will not be titrated. The LR-1 infusion will continue to be titrated based on Burn Navigator recommendations as before.
* **Other rescue procedures:** Procedures such as continuous renal replacement therapy (CRRT), therapeutic plasma exchange (TPE), and/or high-dose ascorbic acid may be employed after patient enrolment. If so, the rationale will be recorded.

**Subject-to-group assignment process:** Subjects will be randomized into one of two study resuscitation conditions (control or plasma) using stratified block randomization according to commonly used procedures (Suresh, 2011). Block randomization is used in randomized controlled trials in order to ensure that the randomly allocated groups are well balanced, especially when sample sizes are small to moderate. In this study, the blocking will be stratified on TBSA categories (e.g., TBSA groups of 20-34%, 35-59%, 60+%) due to the fact that higher burn size is associated with increased risk of ARDS. A stratified block randomization schedule will be developed by the National Data and Statistical Center (NDSC) using the statistical package STATA for clinical centers to use when assigning patients to one of the two treatment groups. This randomization schedule will be coded into a customized REDCap reporting suite. When a new patient is enrolled in the study, center staff will log into REDCap and enter the new patient’s TBSA. The program will be coded such that based on the patient’s TBSA, the lookup table will be consulted and the center staff will receive back a “treatment” or “control” assignment. The randomization schedule will be developed ahead of time based on projected numbers of each TBSA category at each site, but it will be monitored throughout the study to ensure that overall study assignments are approximately even between treatment and control groups. As per IRB stipulations, subjects will have the option to withdraw from the study at any time without compromising clinical care; in such a situation, data collected prior to withdrawal from the study will be maintained and used for analysis.

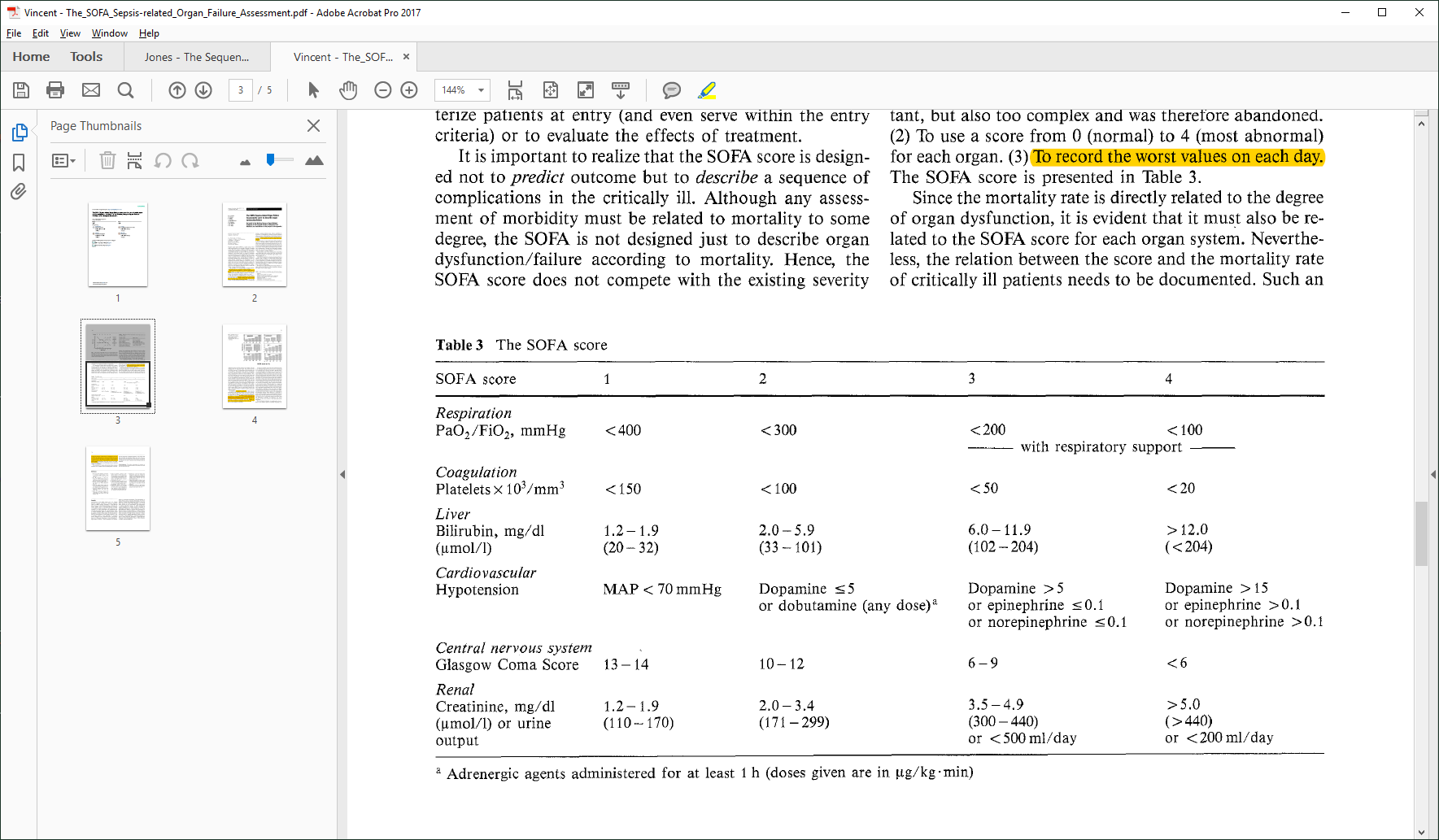
**Figure: First 48 Hours Intervention Flowchart**

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B5.4 Data Collection

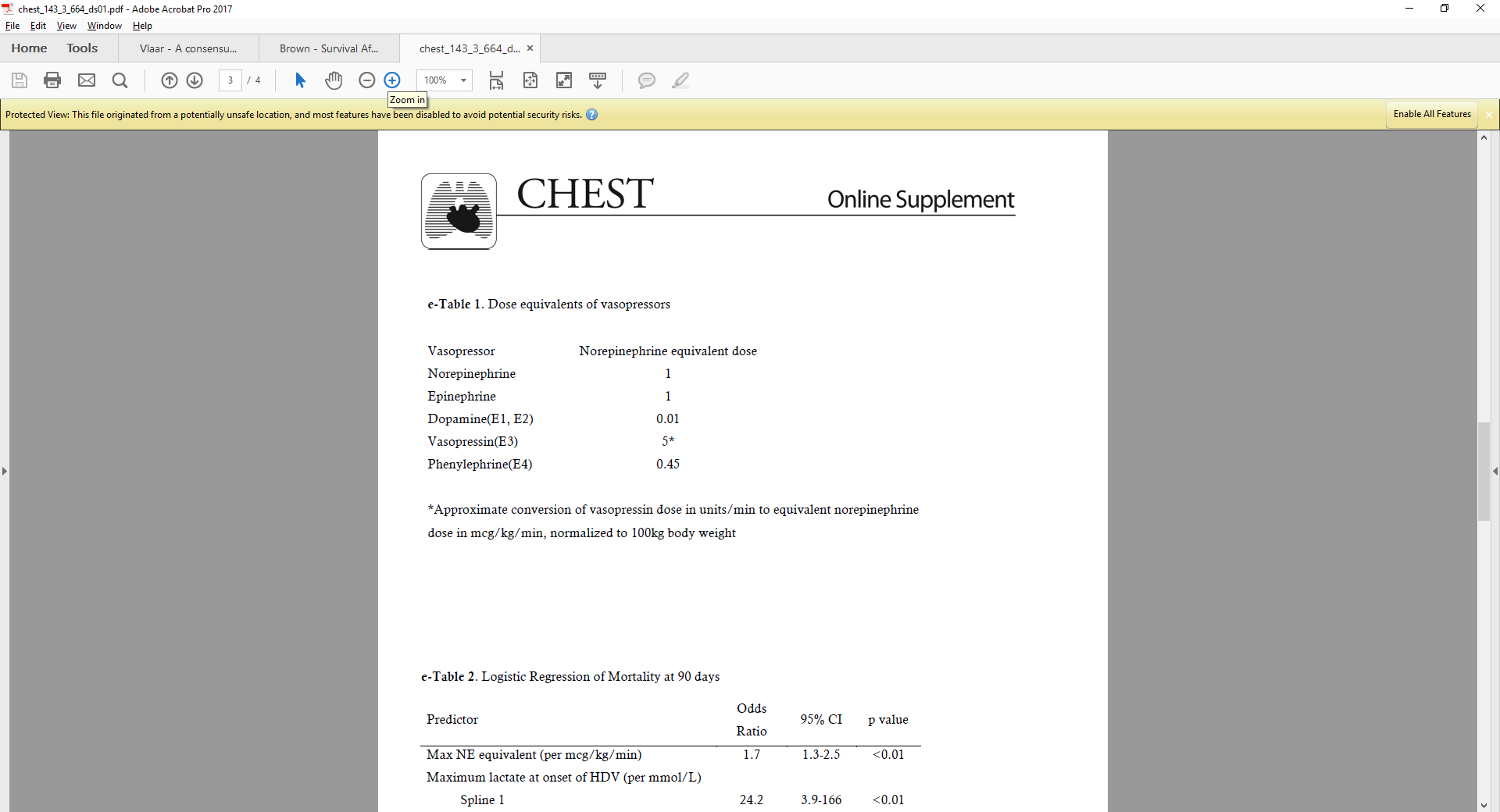
|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Data Element/Variable** | **Source** | **Operational Specification** | **Timing** |
| 1 | Date/time of arrival at burn center hospital, and of BICU admission | Medical Record | As documented by admitting physician | Admission |
| 2 | Date and time of burn | Medical Record | As documented by  admitting physician | Admission |
| 3 | Cause of burn (flame/flash, scald,  contact, other) | Medical Record | As documented by  admitting physician | Admission |
| 4 | Past medical history (describe) | Medical Record | As documented by  admitting physician | Admission |
| 5 | Non-thermal injuries (describe) | Medical Record | As documented by  admitting physician | Admission |
| 6 | Burn size, total (TBSA), % | Lund-Browder Diagram | As documented by  admitting physician | Admission |
| 7 | Burn size, full thickness, % | Lund-Browder Diagram | As documented by  admitting physician | Admission |
| 8 | Burn size, partial thickness, % | Lund-Browder Diagram | As documented by  admitting physician | Admission |
| 9 | Inhalation injury, yes/no | Medical Record | As documented by  admitting physician, using FOB or other method (describe) | Admission |
| 10 | Age, years | Medical Record |  | Admission |
| 11 | Person Sex, male/female | Medical Record |  | Admission |
| 12 | Other injuries | Medical Record | As documented by admitting physician | Admission |
| 13 | Past medical history | Medical Record | As documented by admitting physician | Admission |
| 14 | Current medications | Medical Record | As documented by admitting physician | Admission |
| 15 | Weight, kg | Medical Record | Weigh the patient on  admission | Admission |
| 15b | Height, cm | Medical Record | Height of the patient on  admission | Admission |
| 16 | Heart rate, min-1 | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 17 | Blood pressure, mmHg | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 18 | Mean Arterial Pressure | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 19 | Respiratory rate, min-1 | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 20 | Oxygen Saturation, % | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 21 | Temperature, Celsius | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 22 | GCS, Total | Medical Record |  | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 23 | Arterial blood pH | Clinical lab report | From arterial blood gas  (ABG) | Admission; hours 6, 12, 18,  24, 36, and 48 postburn |
| 24 | Arterial blood PaO2, mmHg | Clinical lab report | Same | Same |
| 25 | Arterial blood PaCO2, mmHg | Clinical lab report | Same | Same |
| 26 | Arterial blood base excess, mmol/L | Clinical lab report | Same | Same |
| 27 | Arterial blood lactate, mmol/L | Clinical lab report | Same | Same |
| 28 | Fraction of inspired oxygen, % | Clinical lab report |  | Same (at time of ABG) |
| 29 | Urine output, ml | Medical Record | From Foley catheter as entered into medical record | Hourly up to 48 hours in burn center |
| 30 | Pre BICU total Fluids infused, ml | Medical Record | Includes prehospital and  ED (specify type of fluids) | Pre-burn center |
| 31 | Pre BICU total output, ml | Medical Record |  | Pre-burn center |
| 32 | LR infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 33 | Pathogen Reduced Plasma infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 34 | 5% albumin infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 35 | 25% albumin infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 36 | Other colloid infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 37 | Other crystalloid infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 38 | Packed red blood cells, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 39 | Total resuscitation volume, ml | Calculated |  | Hours 0-24 in burn center; hours 25-48 in burn center. This will be be calculated through REDCap/DCC process |
| 40 | Enteral nutrition infused, ml | Medical Record |  | Hourly up to 48 hours in burn center |
| 41 | Sodium | Clinical lab report |  | Admission |
| 42 | Potassium | Clinical lab report |  | Admission |
| 43 | BUN | Clinical lab report |  | Admission |
| 44 | Glucose | Clinical lab report |  | Admission |
| 45 | HCO3 | Clinical lab report |  | Admission |
| 46 | Mg | Clinical lab report |  | Admission |
| 47 | iCa | Clinical lab report |  | Admission |
| 48 | Phosphate | Clinical lab report |  | Admission |
| 49 | t. Bilirubin | Clinical lab report |  | Admission |
| 50 | Albumin | Clinical lab report |  | Admission |
| 51 | AST | Clinical lab report |  | Admission |
| 52 | ALT | Clinical lab report |  | Admission |
| 53 | ALP | Clinical lab report |  | Admission |
| 54 | Hgb | Clinical lab report |  | Admission |
| 55 | Hct | Clinical lab report |  | Admission |
| 56 | WBC | Clinical lab report |  | Admission |
| 57 | Platelet Count | Clinical lab report |  | Admission, 12, 24, and 48 hours post burn |
| 58 | PT | Clinical lab report |  | Admission |
| 59 | PTT | Clinical lab report |  | Admission |
| 60 | INR | Clinical lab report |  | Admission |
| 61 | Ventilator Mode | Medical Record |  | Admission |
| 62 | Tidal Volume | Medical Record |  | Admission |
| 63 | Mean Airway Pressure | Medical Record |  | Admission |
| 64 | PEEP | Medical Record |  | Admission |
| 65 | Plateau Pressure | Medical Record |  | Admission |
| 66 | Peak Pressure | Medical Record |  | Admission |
| 67 | Creatinine | Clinical lab report |  | Admission, 24, 48 hour |
| 68 | CRRT performed, 1st 48 h, yes/no | Medical Record | Specify inclusive hours of CRRT | At 48 hours postburn |
| 69 | TPE performed, 1st 48 h, yes/no | Medical Record | Specify inclusive hours of  TPE | At 48 hours postburn |
| 70 | High-dose ascorbic acid infused,  1st 48 h, yes/no | Medical Record | Dose = 66 mg/kg/h.  Specify inclusive hours of infusion | At 48 hours postburn |
| 71 | Mechanical ventilation,  1st 48 h, yes/no | Medical Record | Specify inclusive hours of  mechanical ventilation | At 48 hours postburn |
| 72 | TRALI, first 72 hours, Type I or 2,  yes/no | Medical Record  and TRALI  Worksheet | See Table below | At 72 hours postburn |
| 73 | Norepinephrine equivalents,  1st 48 h | Medical Record  and Vasopressor  Worksheet | See Table below | At 24 and 48 hours postburn |
| 74 | Thromboembolic events, 1st week,  yes/no | Medical Record | Deep venous thrombosis or  pulmonary embolus | At 7 days postburn |
| 75 | Ventilator-free days out of 28 | Medical Record |  | At 28 days |
| 76 | Hospital-free days out of 28 | Medical Record |  | At 28 days |
| 77 | ICU-free days out of 28 | Medical Record |  | At 28 days |
| 78 | In-hospital mortality, yes/no | Medical record |  | At discharge/death |
| 79 | SOFA score | Medical record  and SOFA  Worksheet | See Table below | Admission and each day,  days 1-7 postburn |
| 80 | ARDS 1st week postburn; severity (mild, moderate,  severe) | Medical Record | Berlin criteria | At 7 days |
| 81 | Resuscitation morbidity assessment including documenting any of the following: death; compartment syndrome (abdominal, extremity, ocular); acute kidney injury (Kidney Disease Improving Global Outcomes [KIDGO]); cardiac arrest; myocardial infarction; stroke; bowel infarction. | Medical Record | As documented/diagnosed by physician team | Up to 48 hours post burn  center admission |
| 82 | Syndecan-1 levels | Univ. of MD |  | Admission, 12 h, 24 h,  48 h postburn, |
| 83 | Cytokines IL-6, TNFα, IL-1β,  IL-10, IL-8, GMCSF | Univ. of MD |  | Admission, 12 h, 24 h,  48 h postburn, |
|  | PT, aPTT, factor levels and Rotem | ISR Blood  Coagulation |  | Admission, 12 h, 24 h,  48 h postburn, and infusate |
| 84 | Thrombin-generation assay | Cerus |  | Admission, 12 h, 24 h,  48 h postburn |
| 85 | Discharge Disposition | Medical Record | As documented by discharging physician | Discharge |
| 86 | PROMIS-10 survey | PROMIS-10  Worksheet | See Appendix A | 6 months postburn |
| 87 | Return to work/school/normal activity | TBD |  | 6 months post burn |

Table: SOFA Score Definition



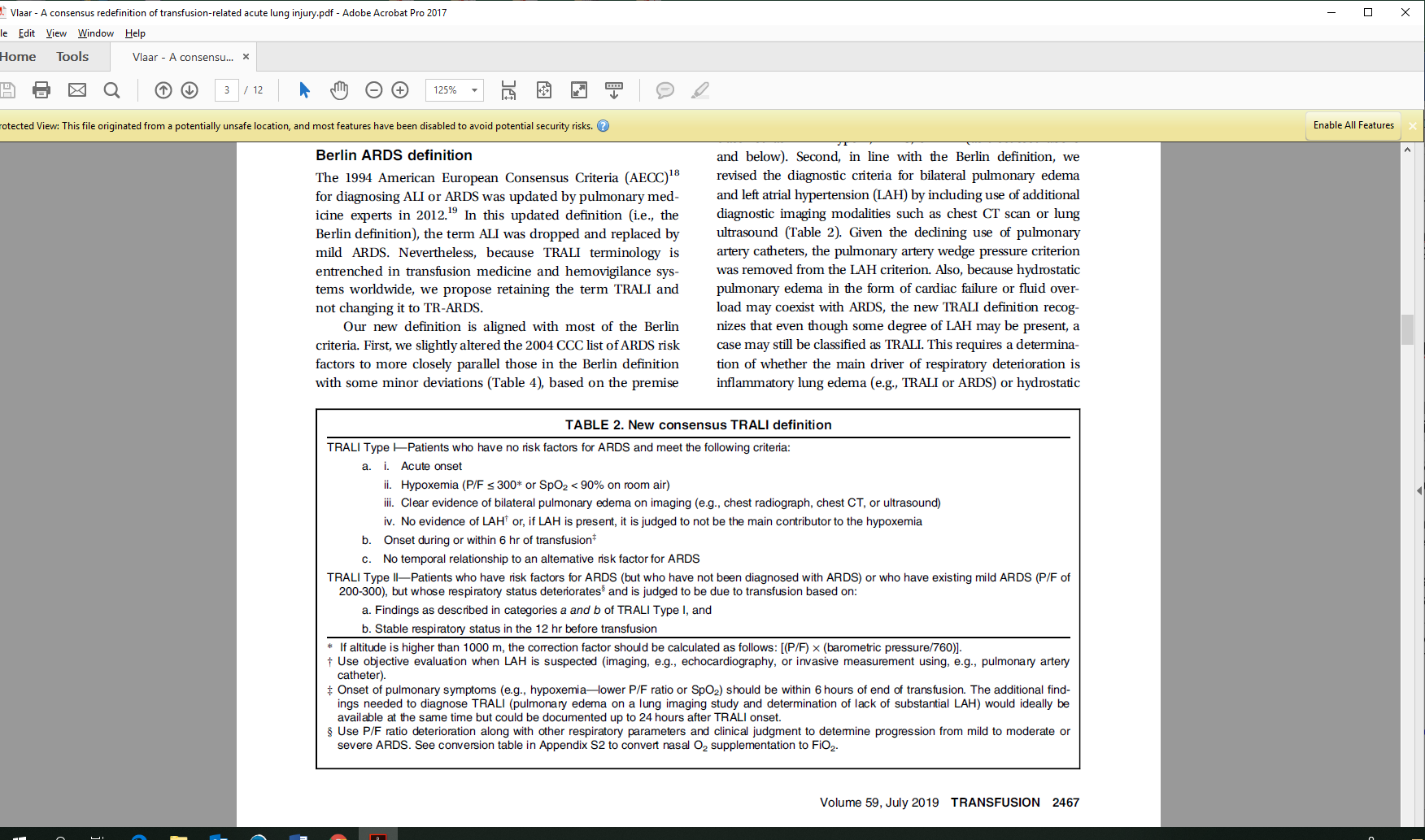
Sequential Organ Failure Assessment (SOFA) is calculated daily using the worst values for the day (Source: Vincent et al., 1996).

Table: Norepinephrine Equivalents



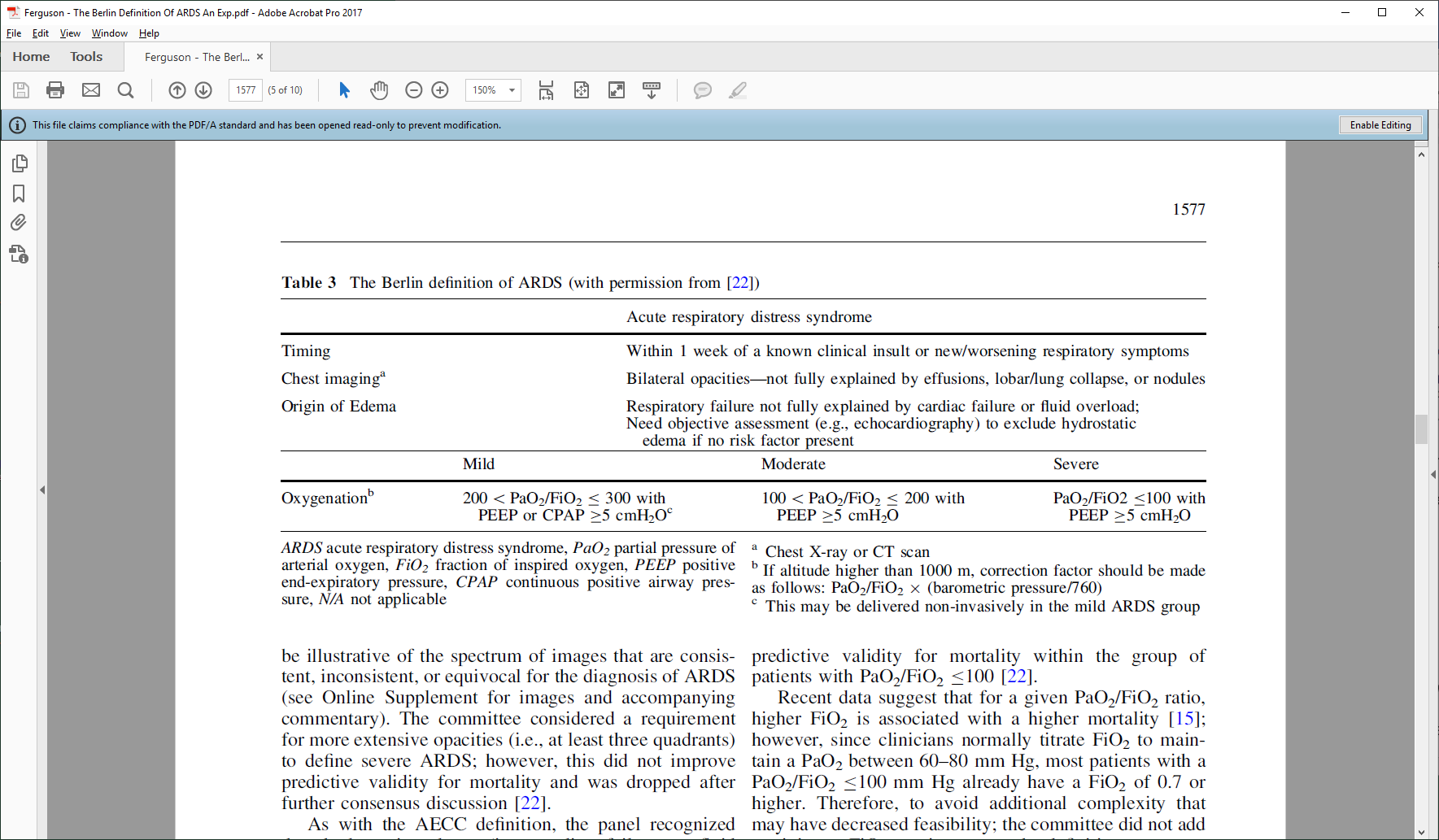
(Source: Brown et al., 2013)

Table: TRALI Definition



2019 Consensus Redefinition of Transfusion Related Acute Lung Injury (TRALI) (Source: Vlaar et al., 2019)

Table: Berlin ARDS Criteria



(Source: Ferguson et al., 2012)

B5.5 Managing Data and/or Human Biological Specimens for this Research

**Data Management**

All data management activities will be carried out by the data center, housed at the University of Washington’s (UW) Department of Rehabilitation Medicine. The data center team currently operates as the data management hub of a multi-center, longitudinal burn outcomes research project, and has expertise in burn research, data management, and state-of-the-art statistical methods. REDCap (Research Electronic Data Capture), developed by Vanderbilt University, will be used as the web-based front-end data collection mechanism for the PROPOLIS project. The front-end of the database will be distributed to all participating data collection centers via a portable and secure browser interface.

Once a potential participant has been identified, approached by the study team, provided consent, and is determined to be eligible during screening, then randomization will occur, identifiers will be collected, and study identification numbers will be assigned. These unique identification numbers will contain a prefix that will identify the ID number by site as well as an individual suffix for each participant. These identification numbers will be used to identify study data, and only the individual center will maintain the link between identification numbers and Personal Health Information (PHI). The study data will be input into REDCap by the data collection staff at each center, and the data center will never have access to either PHI such as name, address, or phone number, or the link between this identifying information and the study data.

The data center at the University of Washington has developed and maintains research databases for many projects. These applications have been reviewed by the University of Washington (UW) Institutional Review Board (IRB), which has found that our infrastructure is secure and provides multiple mechanisms for data confidentiality. We will continue to adhere to our proven methods of data security and controlled access. Working in conjunction with data centers and virtualized host servers operated by UW Information Technology (IT), we engage in regular review processes in order to ensure data security, including hardware-redundant platforms to avoid data loss and minimize downtime.

Confidentiality of sensitive data will be maintained according to four general considerations: (1) physical security of servers and the data stores; (2) security of the data while in transit between sites; (3) proper authentication of all personnel with access to the data, and (4) protection of the data from accidental deletion or corruption. Our approach addresses all four of these factors. Our database and web servers are fully firewalled and secured virtual machines running within an institutionally-managed VM environment. All associated physical equipment is collocated in a 24/7 locked data center with rigid cardkey-based access controls. All physical storage media are fully encrypted at rest by way of self-encrypting solid-state hard disks. The logical network traffic is forbidden to transfer beyond the confines of the subnet containing the database server except with specific domain-based authorization on a per-machine and per-user level. Data from PROPOLIS study centers and the laboratory testing centers will be entered directly into the web-based REDCap database developed specifically for this project and will not be stored on local machines or at any “middle-man.” All browser transmissions including all data and user credentials are transmitted via HTTPS encryption, similar to technologies used by e-Commerce sites. For circumstances where web-based data transfer is not possible or ideal, our organization provides a variety of other technologies for secure transfer of data files, including Secure File Transfer Protocol, signed and encrypted email technologies, or encrypted physical devices.

Access to the data is primarily accomplished through secured web-based protocols between the REDCap browser application and the backend database engine, which helps ensure that queries against the dataset may only be made by authenticated personnel, and, in keeping with tenets of HIPAA policies, are routed through the REDCap history logging feature in order to maintain an audit trail of authorized interactions on a per-field basis. Recent updates to the REDCap have included the addition of a secure messaging platform, enabling project users across geographical boundaries to share information and conversations in an encrypted tunnel provided by the REDCap architecture, reducing the need for less-secure methods such as email or paper mail. Database images are pulled and stored in a secure backup location on a nightly basis, allowing for a controlled data “rollback” to a previous evening in the case of corruption or accidental deletion.

The database itself will be developed by the UW data center, and training in the use of REDCap will be provided to clinical centers by data center staff. REDCap has extensive validation tools, including the ability to set value limits on data items, inability to enter nonsensical data (i.e., for a categorical variable REDCap can be set up in such a way that data that is not one of the item categories cannot be entered), and data quality modules that check data after it has been entered. Once data is collected, each individual clinical center will house the data collected via the paper data collection forms in secured file cabinets, and the UW data center will house the online data in the manner described above.

Hard copies of data collection forms, if used, will be stored in locked storage cabinets separately from signed consent forms and other personal health information such as birth date and identifying information such as name and address. All hard copies of data collection forms will only be identifiable by the linked participant ID number, which each center will maintain the link to separately. Hard copies of specimen testing results, if they exist, will be stored in locked storage cabinets at the testing facilities and will only contain the unique identifier of the subject.

Database locking procedures will include regular data quality checking and cleaning to ensure that the locking process can happen in a timely manner after study completion. The data center staff will develop the database with automatic checks for inconsistencies and illogical entries (i.e., no out-of-range values allowed to be entered, etc.). On the same schedule as the data reporting (see below), data will be cleaned and closely examined for completeness. The data center will schedule the database close-out teleconference with representatives from all participating centers. During the teleconference the locking procedures will be explained, and the data lock checklist/request will be distributed. The purpose of this checklist is to confirm that all mandatory steps have been completed before database lock. Submission of the checklist to the data center will serve as a formal request to lock the database. The lock procedures will begin once a finalized checklist has been received by the Data Center and all steps have been confirmed as being completed. The final review of the data will ensure that all data collected have been entered and there are no unresolved discrepancies including system-generated and manual discrepancies, inconsistencies or questions. If there are any remaining inconsistencies or questions, the Data Center will initiate contact to either discuss the findings or schedule a follow-up conference call. Once the procedures are completed, the Data Center will notify the PI and once approved the Data Center will apply a ‘soft lock’ in which updates to the data can only be made by users that have been granted the ‘privileged update’ permission (typically the PI and the Data Center staff). Datasets will be generated and examined. If no issues are discovered the final database lock will be approved by the PI. All centers will be notified that the database has been locked and data can no longer be added, deleted or modified. The datasets for the primary and secondary papers will generated from the locked database. Data will remain in the locked state until the final manuscript is submitted for publication or the PI decides to unlock the database. Data will be kept for three years after the database is officially locked; at the three-year mark, data will be de-identified, identifiers will be removed, and de-identified data will be kept indefinitely.

Data will be reported by the UW data center regularly (i.e., at least on a quarterly basis, if not more often). A battery of reports will be developed and updated. These reports will then be disseminated across the clinical centers. REDCap will be set up such that data center staff will be alerted if data that indicates an adverse event has occurred has been entered so these incidences can be reported on in a timely manner.

All screening will be based on information in the electronic health record. Because it is not possible to blind the care providers and patient as to the treatment group, all individuals will know whether the subject received plasma. Clinical data and laboratory values collected as part of this study will be extracted from the electronic health record and will be available to the clinical team.

The syndecan-1 levels, thrombin generation assays, and cytokine levels will not be part of the electronic health record and will not be available to the clinical team and the patient. These experimental laboratory tests will not be performed in a laboratory that meets Clinical Laboratory Improvement Amendments (CLIA) federal regulatory standards for clinical laboratory testing and have not been validated as clinically relevant biomarkers and therefore do not present possible benefit to the patient at this time. Additionally, the 6- and 12-month PROMIS10 Global Health Survey results will not be part of the electronic health record and will not be provided to the clinical team or the patient. PROMIS10 has been developed for population level monitoring and to serve as a covariate to account for general health. The score is not intended for clinical purposes and no clinically meaningful cutoffs are available to be used for clinical decision making.

**Human Biological Specimens**

Blood samples will be collected as part of the study at the time of patient enrollment, and at 12, 24, and 48 hours (+/- 1hr). For each timepoint, two blue top tube (sodium citrate 4.5 ml) or four blue top tube (sodium citrate 2.7ml) and one purple top tube (EDTA 4 ml) will be obtained.

Laboratory evaluations are part of Aim 3, to determine if inflammation and/or thrombosis is increased by PRP. Pro and anti-inflammatory cytokines including IL-6, TNFα, IL-1β, IL-10, IL-8 and GMCSF will be measured by Luminex. These will help determine if the intervention is altering systemic inflammation. Rotem®, PT, aPTT and coagulation factors, and thrombin generation will be measured as comprehensive assessments of coagulation status, to assess for a potential prothrombotic state postburn and/or induced by PRP. Lastly, syndecan-1 will be measured by ELISA as an indicator of the endotheliopathy of burns.

Once the blood is drawn into the appropriate tube, the tube should be inverted 3 times to mix the anticoagulant with the blood. The tube will then be centrifuged within one hour of collection at 2000 g for ten minutes. The plasma fraction from each tube will be aliquoted into 2-ml polypropylene tubes labeled with the unique patient identifier and timepoint--for the B (blue) tube at least 600 uL per aliquot and for the P (purple) tube, at least 200 uL. Samples will be stored at -80°C. All samples will be shipped to the ISR on dry ice. UISR ISR will ship plasma samples to Cerus and University of Maryland on dry ice for appropriate analysis of plasma samples. Samples for coagulation (plasma from blue top) will analyzed at the ISR and coagulation analysis will be performed by ISR Blood Coagulation Research Division. Analysis for thrombin generation will be performed at Cerus within 10 minutes of thaw at 37°C using commercially available assays that include quality controls; assays will be run in triplicate. University of Maryland (plasma from purple top) will analyze for syndecan-1 and cytokines which will be run with commercially available assays that include quality controls. ELISA samples will be run in duplicate. Samples shipped on dry ice will be stored in a -80°C freezer upon receipt. Precautions during sample handling will include gloves and eye protection.

CNTR will purchase all shipping materials needed for specimen shipping and distribute to each enrolling site. Training on specimen handling and shipping will be provided via Webex at the beginning of the study and periodically throughout the enrollment period.

**B5.6 Managing Data and/or Human Biological Specimens for Future Research:**Future uses of blood samples from this study will not include DNA or genetic testing. Future testing by investigators of the PROPOLIS team may include additional biomarkers of endothelial function, inflammation, or coagulation that have not yet been identified. Patient consent will include the possibility of these future studies and the option to decline participation.

**B5.7 Devices, Drugs, Dietary Supplements, Nutritional Supplements, And Biologics**

**B5.7.1 Devices**

**5.7.1.1 FDA-approved device being used in this research according to the approved labeling:** Not applicable.

**5.7.1.2 FDA-approved device being used in this research in a manner other than its approved labeling:** Not applicable.

**B5.7.2 Drugs**

**B5.7.2.1 FDA-approved and used in accordance with the approved labeling**: Not applicable.

**B5.7.2.2 FDA-approved and used in a manner not in accordance with its approved labeling**: Not applicable.

**B5.7.2.3 Any drug not approved by the FDA:** Not applicable.

**B5.8 Statistical Analysis**

B5.8.1 Sample Size Estimation

Using an anticipated average fluid resuscitation with the Burn Navigator of 4.2 ml/kg/TBSA and an anticipated goal of 3.0 ml/kg/TBSA, we performed a power analysis with α=0.05 and β = 90% and determined that we require 47 subjects per treatment group (94 subjects total). Each of the 5 participating centers will enroll approximately 19 subjects over 3 years.

**B5.8.2 Data analysis**

Descriptive statistics. Descriptive statistics will be calculated to describe participants’ demographic characteristics, injury characteristics and all other constructs (e.g. volume of resuscitation fluids, incidence and length of hemodynamic instability, compartment syndrome) and their dimensions. The analysis plan includes examining baseline differences between the 2 groups with Fisher’s exact test, t-tests, or Wilcoxon tests, depending on whether the variables being analyzed are categorical or continuous. Distributions of all variables will be examined for outlying values and skewness, and, where indicated, variables will be recoded or transformed as necessary for conducting study aim-related analyses. The choice of transformation (e.g., square root or logarithmic) will depend on the shape of the distribution. If transformation does not produce a distribution that is appropriate for parametric statistical analyses, we will use nonparametric procedures (i.e. Wilcoxon rank tests and non-parametric regression). All aim-related outcomes will be analyzed under the principle of intent to treat (ITT), thus including all outcome data regardless of a participant’s adherence to the protocol.

Analyses for Aims

Specific aim 1: To determine whether the Treatment Group and Control Group are different with regards to total volume of all resuscitation fluids, differences will be tested in several ways. At each of 2 timepoints (24 and 48 hours) we will use either t-tests or non-parametric Wilcoxon rank tests, if appropriate given the distribution of the data, to determine significant differences. In addition, we will utilize linear regression analyses with fluid volume as the independent outcome and group membership (Treatment or Control) as a predictor. In these analyses we will adjust for potential confounders, including but not limited to TBSA, gender, and study site. All analyses will examine model assumptions and model fit.

Specific aim 2: To determine whether the groups are different with respect to ARDS incidence and severity we will compare the groups at discharge from hospital. We will do a preliminary chi-square test to compare the 2 groups based on either no, mild, moderate, or severe ARDS experienced during their hospital stay. This will be followed by ordinal logistic regression to determine if treatment group predicts development and severity of ARDS after adjusting for potential confounders, including % TBSA, inhalation injury and gender. To account for variance across multiple sites and care providers in the study, site will also be included as a predictor in the model. The proportional odds assumption will be examined as well as other model assumptions and model fit. If necessary, we will classify patients into ARDS (+) and (-) groups and conduct logistic regression and Fisher’s exact tests to examine differences. We will use logistic regression to examine if treatment group affects development of TRALI.

Secondary outcome measures will be examined at discharge (duration of ventilation, length of ICU, SOFA scores, and ICU and hospital stay), 30 days (ventilation-free days), or 6 and 12 months post-injury (PROMIS mental and physical) by conducting either t-test analyses or rank tests as appropriate, depending on if the outcomes are normally distributed. Mortality will be examined by comparing treatment groups using logistic regression, adjusting for TBSA and treatment site.

Specific aim 3: Again, to determine whether the Treatment Group and Control Group are different with respect to biochemical assays, end-points will be tested in several ways. First, descriptive statistics will be calculated for each group. Differences will be tested between the groups for syndecan 1, thrombin, IL-6, TNFα, IL-1β, IL-8, IL-10, and GMCSF levels at each timepoint using univariate comparison tests such as t-tests or non-parametric tests if appropriate given the distribution of the data. Generalized linear mixed models with an unstructured covariance matrix will then be estimated using all timepoints (baseline, 12 hrs, 24 hrs, 48 hrs). The intervention group will be treated as a between-subjects factor and time as a within-subjects factor. In these analyses, group membership (e.g., treatment or control), personal (e.g., gender) and burn factors (e.g., TBSA) will be the independent variables. Similar to the other analyses, to account for variance across multiple sites and care providers in the study, site will also be included as a predictor in the model.

SECTION C: HUMAN RESEARCH PROTECTIONS

**C1. RECRUITMENT AND CONSENT**

**C1.1 Identification and Selection of Subjects:** Subjects will be recruited for this study following admission to one of the participating sites for the treatment of acute burn injury. On admission to a participating Burn Center, the patient will be assessed by the clinical care team as to potential eligibility for enrollment in this study. With consideration for the Health Insurance Portability and Accountability Act (HIPAA) regulations, as interpreted by the site’s institution, the PI/study coordinator may access the hospital’s electronic medical records, if necessary, to identify potential candidates for screening and enrollment. Obtaining informed consent prior to initiation of any procedures to determine eligibility is not possible given the nature of this study. Therefore, each study site will submit a waiver of authorization for use and disclosure of protected heath information as part of the human subjects review application.

**C1.2 Recruitment Process:** If the patient is deemed potentially eligible, a member of the patient’s care team will obtain oral approval from the patient or a legally authorized representative for research personnel to discuss possible study participation. This study will not use recruitment or advertising materials. Subjects will not be compensated for participation. Since the care teams/providers assist in identifying potential subjects, each site will ensure that they have the necessary competency, confidence and information to complete this activity. Clinical care teams/providers on the units most likely to provide care to burn patients will be oriented to the study during staff meetings. They will learn the inclusion and exclusion criteria so that they can recognize potentially eligible patients in a timely manner. They will also be trained on how to introduce the study to the patient or legally authorized representative. They will have readily available contact information for the research study team member who is available to enroll the subject and to address any study-related questions or concerns. The site research teams will work with the clinical care teams to address any systemic barriers to timely enrollment and data collection.

**C1.3 Eligibility:** Eligibility will be determined by means of a checklist. See above for inclusion and exclusion criteria. Data for determination of eligibility will be obtained during screening by participating site study personnel. The data will be obtained from the medical record and by interviewing the patient and the LAR.

**C1.4 Consent Process:** Patients who are deemed potentially eligible will meet with a research nurse or coordinator. (For patients unable to provide consent, a legally authorized representative will be approached as described in the following paragraphs.) The research coordinator will explain the study and obtain informed written consent and HIPAA authorization as approved by the Human Subject Division. The consent process will occur within 8 hours of injury. The patient will be asked to read the consent form, or it will be read to them by the study investigator or staff member. If the patient cannot read or sign for themselves, an impartial witness must witness the consent form and sign and date the form. A verbal explanation will be provided in terms suited to the participant’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Patients will be given adequate time to consider participation and/or discuss participation with others. If the patient requires more time than is allowed by the research design, they will not be enrolled. Patients will be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. In compliance with Title 10 United States Code Section 980 (10), the intent for the study to provide benefit to the patient will be clearly described in the consent form.

Consent form: As this study will contract with Western Institutional Review Board (WIRB) for services as the single site IRB for this study, a WIRB template of the adult consent form will be used. The template was modified as appropriate for this study and Department of Defense-required language is included.

C1.4.1 Research involving subjects with cognitive impairment or who lack capacity to provide informed consent: If the patient is not able to provide consent due to altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation or anesthesia, brain injury, or stress/life situations, the investigator or research staff member will approach a legally authorized representative (LAR) in accordance with 45 CFR 46.102(c) and 21 CFR 50.3(l). Each site will define how they will determine which individuals meet the criteria for being a LAR under their local, state/provincial and federal law with advice from their institution’s legal counsel. In this case, the research nurse or coordinator will re-approach the patient and obtain written consent when cognition and ability to consent has returned to normal. A verbal explanation will be provided in terms suited to the LAR’s comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. LARs will be given adequate time to consider participation and/or discuss participation with others. If the LAR requires more time than is allowed by the research design, the patient will not be enrolled. LARs will be informed that participation is voluntary and that the patient may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the LARs for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed. The rights and welfare of the participants will be protected by emphasizing to LAR that the quality of their medical care will not be adversely affected if they decline to participate in this study. In compliance with Title 10 United States Code Section 980 (10), the intent for the study to provide benefit to the patient will be clearly described in the consent form.

C1.4.2 Research involving non-English speaking subjects

As appropriate to the local population, sites will have approved translated consent forms and speakers/translators for the most commonly spoken languages.The consent form will be translated into Spanish (using WIRB-certified translation). If the patient or LAR prefers to communicate in Spanish, a Spanish-speaking study staff member or hospital translator will conduct the consent process. As appropriate by site, the consent form will be translated into other languages and presented by translators in order enroll non-English/Spanish speaking patients. All sites will have mechanisms for ongoing communication with the subject throughout the research and in case of emergency. Sites will ensure at least one member of the research team is fluent in the language, and that research staff member(s) will be available during emergencies; or ensure the research team has 24-hour access to a translation service with sufficient medical expertise to discuss the research.

C1.4.3 Research involving a waiver of the requirement to obtain informed consent OR alteration of the elements of informed consent*:* Not applicable.

**C1.4.4** **Research involving a** w**aiver of the requirement for investigator to obtain a signed consent form:** Not applicable.

C1.4.5 Waivers of assent or parental permission when the research involves children: Children will not be enrolled in this study.

**C1.4.6** **Research involving data collection for the** **USAMRMC Volunteer Registry Database:** Not applicable.

**C2.COMPENSATION FOR PARTICIPATION**: There will be no compensation for participation in this study.

**C3.WITHDRAWAL FROM RESEARCH PARTICIPATION**

Subjects may withdraw from the study at any time by communicating to the research team. All data collected prior to withdrawal will be kept for analysis.

**C4. PRIVACY FOR SUBJECTS**:See above, para. B5.5, Data Management.

**C5. CONFIDENTIALITY PROCEDURES FOR RESEARCH RECORDS, DATA, HUMAN BIOLOGICAL SPECIMENS:**See above, para. B5.5, Data Management.

**C6. RISKS OF HARM, MEASURES TO REDUCE THE RISKS OF HARM, AND BENEFITS OF PARTICIPATION**

**C6.1 Risks of Harm**

*Research Procedure Name:* Fluid resuscitation

*Research Procedure Description:* Patients will receive fluid resuscitation based on one of two strategies; crystalloid-based or plasma-based.

*Research-related Risks:* Fluid resuscitation is the standard of care for patients with burn shock. There may be risks associated with either arm of the study. Based on available data, patients in the crystalloid arm may be at higher risk for volume overload (infusion of a large volume of fluid during the resuscitation phase of care), to include acute respiratory distress syndrome (ARDS). Patients in the plasma arm may be at higher risk of transfusion-related complications such as TRALI (transfusion-related acute lung injury). In brief, both groups of patients may be at risk of lung injury. It is not possible to determine which group is at higher risk; ascertaining this risk is a major aim of the study.

*Measures to Minimize Risks of Harm: (Precautions, safeguards):* Both arms of the study will provide the clinician and study team with the ability to rescue the patient to other resuscitation strategies, to include the initiation of albumin. Albumin is a common rescue strategy during burn shock resuscitation.

*Research Procedure Name:* Plasma infusion

*Research Procedure Description:* Patients in the plasma arm will receive plasma.

*Research-related Risks:* There is a small but finite risk of disease transmission when infusing any blood product.

*Measures to Minimize Risks of Harm: (Precautions, safeguards):* The use of the FDA-approved INTERCEPT system for pathogen reduction is intended to further reduce the risk of disease transmission.

*Research Procedure Name:* Blood draws

*Research Procedure Description:* Blood will be drawn at several times in order to perform various study-related assays.

*Research-related Risks:* Blood draws could be associated with pain from a needle stick and with loss of blood.

*Measures to Minimize Risks of Harm: (Precautions, safeguards):* Blood will be obtained from central venous or arterial catheters in order to obviate the need for any additional needle sticks. For a patient with a major burn injury, the additional volume represented by these blood draws is negligible.

*Research Procedure Name:* Data collection.

*Research Procedure Description:* Data will be collected as described elsewhere in this protocol.

*Research-related Risks:* Loss of confidentiality.

*Measures to Minimize Risks of Harm: (Precautions, safeguards):* See above, paragraph C5, Confidentiality Procedures.

**C6.2 Incidental or Unexpected Findings:** Incidental or unexpected findings will be communicated in writing to the clinical team for inclusion in the patient’s medical record (to include in the discharge summary or equivalent document). This information will be disclosed verbally and in writing to the patient, no later than at the time of discharge from the hospital.

C6.3 Potential Benefits: Possible benefits to all patients enrolled in this study include lower complications related to fluid resuscitation. All patients will benefit from the additional training provided to bedside nurses and physicians in burn shock fluid resuscitation, to include, but not limited to, how to use Burn Navigator, a burn resuscitation decision support system. In particular, use of decision support for burn resuscitation was associated with a significant reduction in the total amount of fluid infused, as well as in ARDS rates and mortality (Salinas et al.). The benefits of using Burn Navigator will accrue to both arms of this study. In addition, all patients will potentially benefit from routine, scheduled monitoring of certain key parameters such as lactate and base deficit, which are associated with outcomes during burn shock resuscitation. All patients will potentially benefit from early and continual screening and assessment for conditions including organ failure (SOFA scores, ARDS diagnosis). Possible benefits to others include improved resuscitation and outcomes after burn injury in the future.

**C7. DATA AND SAFETY MONITORING**

C7.1 Monitoring

A Data Safety Monitoring Board will be constituted for this study. This committee will review and approve the protocol. They will also identify logistic problems that may pose problems with early randomization, patient accrual and retention, participant safety, data collection and follow-up. The DSMB will be governed by a charter. The DSMB will help ensure the safety of the trial by monitoring adverse outcomes, reports of unanticipated problems involving risk to participants, serious adverse events and death events as they occur. The DSMB will meet semi-annually and review subject records to ensure that appropriate mechanisms to protect the safety of study participants are followed, that protocol requirements are adhered to, and that data are accurate, complete, and secure

C7.2 Research Monitor (as applicable): A medical monitor for the overall study has been appointed (COL Kevin K. Chung, MD, Chair, Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, kevin.chung@usuhs.edu.)

C8. REPORTABLE EVENTS

C8.1 Expected adverse events

Common expected AE’s/SAE’s will include: compartment syndrome, multi-organ failure, acute respiratory distress syndrome, pneumonia, wound infection, urinary tract infection, blood stream infection, acute kidney injury requiring hemodialysis, and death (if Baux Score >100).

Adverse Events Reporting Procedure – All adverse events will be classified by: a) Severity (mild, moderate, severe); b) Expected vs Unexpected; and c) Related vs Unrelated. Unrelated adverse events, not of study interest will not be recorded on the subject’s Adverse Events Log or entered into the eCRF. Only study-related adverse events or events that are outcome measures of interest that occur during the study period (after randomization until study conclusion) will be recorded.

C8.2 Unexpected adverse events and unanticipated problems

Serious Adverse Events will include potential transfusion-related acute lung injury, thromboembolic events, transfusion reactions, and death (If Baux Score < 100). SAE reporting for this study will follow local reporting procedures with clinical sites will notifying the DCC of a SAE within 3 business days of discovery of the event. Site investigators will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). UP’s that are serious adverse events will be reported to the single IRB and to the DCC within one day of the investigator becoming aware of the event. Any other UP will be reported to the single IRB and to the DCC within one day of the investigator becoming aware of the problem

C8.3 Adverse device effects: Not applicable.

C8.4 FDA-regulated research under IND and IDE: Not applicable.

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**SECTION E: ABBREVIATIONS AND ACRONYMS**

ABA: American Burn Association

ACS: abdominal compartment syndrome

AECC: American-European Consensus Conference

AKIN: Acute Kidney Injury Network

ARDS: acute respiratory distress syndrome

CNTR: Coalition for National Trauma Research

CRRT: continuous renal replacement therapy

DSMB: Data Safety Monitoring Board

ECS: extremity compartment syndrome

EVLW: extravascular lung water

FOB: fiberoptic bronchoscopy

FDA: US Food and Drug Administration

FFP: fresh frozen plasma

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIPAA: Health Insurance Portability and Accountability Act

ICU: Intensive care unit

IRB: Institutional Review Board

ISS: Injury Severity Score

LAR: legally authorized representative

LR: lactated Ringer’s solution

MAP: mean arterial pressure

NTI: National Trauma Institute, i.e., Coalition for National Trauma Research

NYHA: New York Heart Association

PHI: Personal Health Information

PI: Principal Investigator

PR: pathogen-reduced

PROMIS10: Patient-Reported Outcomes Measurement Information System global health short form

PROPOLIS: Plasma Resuscitation without Lung Injury trial

PROPPR: Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial

PRP: pathogen-reduced plasma

REDCap: Research Electronic Data Capture

SOFA: Sequential Organ Failure Assessment score

TBSA: total body surface area burned, percent

TPE: therapeutic plasma exchange

TRALI: transfusion-related acute lung injury

UO: urine output

USAISR: US Army Institute of Surgical Research

UW: University of Washington

WIRB: Western IRB

**SECTION F: DoD PRIVACY RULE AND PROTECTED HEALTH INFORMATION (HIPAA)**

*Click in the appropriate box See the “Guide for Investigators” for definitions and further information.*

NA – institution is not a covered entity

NA – will not use or disclose protected health information

HIPAA authorization will be obtained

An application for waiver/alteration of HIPAA authorization will be submitted

Appendix A. PROMIS-10

