Plasma for burn shock resuscitation: is it time to go back to the future?

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Patients with burn shock can be challenging to resuscitate. Burn shock produces a variety of physiologic derangements: Patients are hypovolemic from volume loss, have a increased systemic vascular resistance, and may have a depressed cardiac output depending on the extent of the thermal injury. Additionally, the burn wound produces a significant inflammatory cascade of events that contributes to the shock state. Fluid resuscitation is foundational for the initial treatment of burn shock. Typical resuscitation is with intravenous lactated Ringer's in accordance with well-established formulas based on burn wound size.

In the past century, as therapies to treat thermal injuries were being developed, plasma was the fluid used for burn resuscitation; in fact, plasma was used in World War II and throughout the 1950s and 1960s. Plasma was abandoned because of infectious risks and complications. Despite huge strides in transfusion medicine and the increased safety of blood products, plasma has never been readopted for burn resuscitation. Over the past 15 years, there has been a paradigm shift in trauma resuscitation: Less crystalloid and more blood products are used; this strategy has demonstrated improved outcomes. Plasma is a physiologic fluid that stabilizes the endothelium. The endotheliopathy of trauma has been described and is mitigated by transfusion strategies with a 1:1 ratio of RBCs to plasma. Thermal injury also results in endothelial dysfunction: the endotheliopathy of burns. Plasma is likely a better resuscitation fluid for patients with significant burn wounds because of its capability to restore intravascular volume status and treat the endotheliopathy of burns.

Patients with significant thermal injury represent a unique population. Unlike other life-threatening conditions such as sepsis, hemorrhage, anaphylaxis, and traumatic injury—in which initial therapy results in reversal of physiologic abnormality and improvement in clinical status—burn resuscitation frequently results in ongoing physiologic derangement. Thermal injury leads to disruption of homeostasis secondary to local and systemic inflammatory responses culminating in "burn shock," a unique pathophysiologic process characterized by intravascular volume depletion, low pulmonary artery occlusion pressure, increased systemic vascular resistance, and depressed myocardial contractility. Fluid administration is the cornerstone of effective resuscitation, with the goal of restoring intravascular volume and perfusion. The type, quantity, duration, and endpoints of burn shock resuscitation have been debated over the past century; however,

ABBREVIATIONS: ACS = abdominal compartment syndrome; ARDS = acute respiratory distress syndrome; FFP = fresh frozen plasma; LR = lactated Ringer's solution; TBSA = total body surface area; USAISR = US Army Institute of Surgical Research.

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resuscitation without morbidity remains a significant challenge. This review will highlight the ongoing challenges in the resuscitation of burn patients and reintroduce plasma resuscitation, both as a volume expander and as a way of ameliorating postburn endothelial injury.

Appropriate fluid management is critical to the survival of patients with burn injuries. Large burn wounds are fatal if not treated; before the 1950s, hypovolemic shock or shock-induced renal failure was the leading cause of death after thermal injury.[1] From the current understanding of the massive fluid shifts and vascular changes that occur with thermal injury and the initiation of fluid resuscitation shortly after injury, early mortality has decreased considerably. The concepts of "burn shock" and "burn edema" were better understood after the Cocoanut Grove fire in 1942, and fluid resuscitation based on body weight was conceptualized.[2] In 1952, Evans developed the first formula for burn resuscitation that took burn total body surface area (TBSA) and body weight into account; this formula became one of the first straightforward formulas for computing the fluid replacement in a burn casualty.[2] Surgeons at the Brooke Army Medical Center in San Antonio, Texas, modified the original Evans formula of normal saline 1.0 mL/kg/%TBSA + colloid 1.0 mL/kg/%TBSA to normal saline 1.5 mL/kg/%TBSA + colloid 0.5 mL/kg.[1,2] Later, secondary to studies by Pruitt, the modified Brooke formula became 2.0 mL/kg/%TBSA of LR. The Parkland formula has been considered by many to be a "gold standard" for burn shock resuscitation. It was developed by Dr. Charles Baxter at Parkland Hospital in the 1960s. It remains one of the most commonly used formulas today. The Parkland formula calls for LR to be administered at 4.0 mL/kg/%TBSA, with one-half of the volume administered within the first 8 hours. The modified Brooke formula and the Parkland formula are the most common resuscitation strategies used today; however, there is a large amount of heterogeneity, and the burn community lacks a prospective randomized clinical trial to inform the best resuscitation strategy for early and late outcomes.

DEFINING THE PROBLEM: BURN SHOCK REQUIRES SIGNIFICANT RESUSCITATION

The resuscitation of patients with extensive burns, that is, greater than 20% TBSA, is a significant challenge. Both overresuscitation and underresuscitation lead to potentially devastating complications or even death. Overresuscitation is a major source of morbidity and mortality for burn patients and can result in pulmonary edema, myocardial dysfunction, conversion of superficial to deep burns, need for fasciotomies in unburned limbs, and abdominal compartment syndrome. Effective restoration of volume status in burn shock does not immediately achieve complete normalization of physiologic variables, as the burn injury leads to ongoing cellular and hormonal responses.

The pathophysiology of burn shock has been fairly well defined, but effective intervention strategies are mainly limited to various intravenous fluid regimens. The primary process that drives burn shock is a derangement of the Starling forces across the microvasculature.[1] 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 throughout the duration of burn shock.

HISTORY OF BURN SHOCK RESUSCITATION

Prior to World War II, the primary treatment for burns was topical, and the lethality of burn shock was very high. World War II was a turning point for burn resuscitation. While whole blood had been used as a resuscitation fluid for bleeding from traumatic injury during World War I and the Spanish Civil War, plasma was introduced in 1936 as a substitute for whole blood. Both liquid plasma and freeze-dried plasma were used early in World War II as part of the "Blood for Britain" campaign in the United States, with over 14,000 units of blood donated and thousands of these processed into plasma units. Sterilization challenges and contamination of pooled plasma with hepatitis virus resulted in the cessation of this initiative in the early 1950s.[79] Before World War II, in anticipation of the war, the United States had made a national commitment to supporting medical research of military relevance to include chemotherapeutics, surgical care, and resuscitation. A prominent example of the use of plasma for burn shock resuscitation was provided following the mass casualty disaster at the Cocoanut Grove nightclub in November 1942. In that instance, plasma was delivered by the blood bank at the Massachusetts General Hospital to the bedside diluted half and half with normal saline; the assumption is that this was lyophilized plasma; however, the literature is not clear why is was diluted with normal saline. During World War II, widespread availability of plasma enabled it to play a prominent role in the resuscitation of combat casualties.[78,79]

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.[2] Reiss et al.,[3] at the US Army Institute of Surgical Research (USAISR) and Brooke General Hospital, described the original Brooke formula, which provided 0.5 mL/kg/TBSA of plasma and 1.5 mL/kg/TBSA of normal saline. 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. There has not been a controlled trial to assess the outcomes of these resuscitation strategies.

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.[4–6] The 1968 study that demonstrated the need for isotonic crystalloid solutions in the initial resuscitation of severe burns to resuscitate the extracellular fluid space included 11 thermally injured human patients as well as dog models, 12 in each study cohort. Much of the subsequent focus on crystalloid resuscitation can be attributed to this theoretical basis, to include the initial 2-L bolus prescribed by 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 after the burn. The Parkland (or Baxter) formula called for 4 mL/kg/TBSA burned over the first 24 hours, all of it LR.[5] The modified Brooke formula called for 2 mL/kg/TBSA burned during the first 24 hours, again all of it lactated Ringer's (LR).[7] Colloid use, as 5% albumin at a dose of 0.3 to 0.5 mL/kg/TBSA, was postponed until hours 24 to 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 after the burn did not influence the rate of plasma volume loss.[7] 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 versus LR for burn shock resuscitation was subsequently published in 1983 by Goodwin et al.,[8] also from the USAISR. 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 using the dual-indicator dilution technique, and found that the albumin group developed a higher extravascular lung water. 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 that demonstrated no change in pulmonary microvascular permeability.[9] 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 until hours 24 to 48 after the burn.

Over the ensuing years, 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.[10,11] 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 5% albumin could be used as a "salvage" therapy beginning about 8 hours after the burn, 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 fresh frozen plasma (FFP), as proposed herein. A systematic review by Dubois in 2017 looking at albumin administration during the fluid resuscitation phase of burn patients and mortality found a paucity of high-quality studies looking at albumin or FFP. The authors concluded that there was limited evidence in the literature and no high quality trial to assess the impact of albumin solutions on the mortality of burn patients.[76] There remains no high-quality evidence supporting or refuting the use of FFP as a resuscitation product in burn patients.

THE CONUNDRUM: UNDERRESUSCITATION AND SHOCK VERSUS "FLUID CREEP" AND OVERRESUSCITATION

It was well established that the primary goal of resuscitation in burn patients was to maintain adequate end-organ perfusion by using intravascular, sometimes large-volume, fluid resuscitation. Before the importance of fluid resuscitation in thermal injury was understood, patients with moderate-size burn wounds would survive the inciting event only to succumb to shock in the first 24 hours, and approximately 30% of survivors developed renal failure. Underresuscitation results in a continued shock state, suboptimal tissue perfusion, and ischemic end-organ injury and renal failure. After the importance of volume resuscitation was recognized as a crucial therapy for burn patients, multiple formulas to guide fluid resuscitation emerged, and while underresuscitation has become relatively uncommon, the phenomenon of fluid creep appeared.

Fluid creep occurs when the volumes actually delivered greatly exceed the formula predictions.[12] In a review of the use of the modified Brooke formula at the USAISR, Cancio et al.[13] found that patients actually received 4.9 mL/kg/TBSA. Similarly, Cartotto and Zhou[14] found that patients started on the Parkland formula received 6.3 mL/kg/TBSA. There is one retrospective study comparing the two formulas. Chung et al.[80] documented that combat casualties who were started on the modified Brooke formula on average received 3.8 mL/kg/TBSA; whereas those who were started on the Parkland formula on average received 5.9 mL/kg/TBSA. These authors concluded that "fluid begets more fluid." A

pathophysiologic explanation would be 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.

The cause of fluid creep is likely multifactorial. Lack of experience and inadequate attention to detail may play a role. 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.[14,27] 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*.[28] The effect of more opioid use during burn shock is to increase the likelihood of hemodynamic instability and thus fluid needs.[29] Possibly, changes in the medical fitness of the population, with an increased incidence of diabetes and substance addiction, may also affect fluid needs.[30]

In a thorough evaluation of the literature, Guilabert et al.[77] performed a nonsystematic review to help determine the current evidence and recommendations for the early resuscitation of burn patients. In their review, published in the *British Journal of Anaesthesiology* in September 2016, they observed that many burn units based their resuscitation practices on formulas that were almost 50 years old despite the advances in hemodynamic monitoring. The authors assessed 92 articles, 19 of which were included in their review. The authors concluded that, based on the studies, the initial resuscitation fluid should be a balanced crystalloid and that colloids are inappropriate during the first hours because of the increased capillary permeability; they indicate that plasma may have a role in burn resuscitation but that the data are limited and additional evidence is needed. Overall, there has been a paucity of high-quality prospective studies to determine the best resuscitation fluid in the early period after thermal injury.

OVERRESUSCITATION: A POTENTIALLY DEADLY COMPLICATION OF FLUID CREEP

The term *fluid creep* was accompanied by increased recognition of complications (termed *resuscitation morbidity* by Wolf)[31,34] which ranged in severity from difficult to disastrous. Zak and colleagues[15] showed that smaller children with larger burns, even in the absence of inhalation injury, risked edema of the airway and a need for intubation. There are several reports on the relationship between fluid resuscitation and acute respiratory distress syndrome (ARDS) in burn patients. Fluid resuscitation data on 72 burn patients from the Glue Grant showed that average volume received was 5.2 mL/kg/TBSA, and increased volume was associated with pneumonia, bacteremia, ARDS, multiple organ failure, and death.[16] A larger analysis by Mason et al.[17] of 330 Glue Grant patients recently confirmed the relationship between resuscitation volume and ARDS. Patients were categorized by volume of resuscitation with LR 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 group 42% ($p = 0.003$). Ivy et al.[18,19] described abdominal compartment syndrome (ACS) in patients who received more than 250 mL/kg during the first 24 hours. Subsequent articles have corroborated the relationship between large-volume fluid resuscitation and ACS and have documented high mortality despite decompressive laparotomy.[20]

ACS is not the only compartment-related consequence of overresuscitation. Surgeons at the USAISR wrote about extremity compartment syndrome (ECS) in burn patients,[21] and identified ECS in unburned extremities following large-volume resuscitation.[22] Sullivan and colleagues described orbital compartment syndrome in burn patients receiving an average of 9 mL/kg/TBSA.[23] Insofar as timely wound healing (e.g., successful skin grafting) is a sine qua non for survival after a major burn,[24] the deleterious effect of edema on wound healing[25] is one of the strongest arguments against overresuscitation. Indeed, Liu and colleagues[26] published a predictor of open wound size, which incorporates four variables: TBSA, fluid resuscitation volume, postburn day, and age.

EFFORTS TO CONTROL FLUID CREEP AND OVERRESUSCITATION

The most common rescue therapy for the runaway resuscitation 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 et al.[31] recommended calculating the projected 24-hour fluid resuscitation volume at postburn hour 12.[32] If this volume was 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). At the University of Michigan, Park et al.[33] 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.

The most well-known protocol for "albumin rescue" was described by Saffle.[34] In that algorithm, resuscitation is started at the Parkland rate. The main trigger for initiating albumin is an hourly crystalloid rate that is twice the calculated rate for 2 hours. 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.[35] Dulhunty and coauthors[36] from Brisbane studied 80 patients with TBSA greater than 15%. Higher fluid resuscitation volume was associated with pneumonia and extremity compartment

syndrome, whereas colloid use (type of colloid not specified) during the first 24 hours reduced compartment syndrome risk.

Consistent with the above findings, in 2009 Greenhalgh[37] published the results of an International Society for Burn Injuries/American Burn Association survey of burn resuscitation practice which, while mentioning the Parkland formula as the preferred formula and LR as the preferred solution, also included the initiation of colloid during the first 24 hours by 49.5% of respondents. Another international survey of burn resuscitation practice, carried out by the European Society of Intensive Care Medicine 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 urine output, fixed TBSA (e.g., >30%), ARDS, systematically 6 to 8 hours after injury, and inhalation injury.[38] A prospective multicenter observational study of resuscitation, to include albumin use, is currently ongoing (Acute Burn Resuscitation Multicenter Prospective Observational Trial, or [ABRUPT]; NCT03144427, clinicaltrials.gov). A randomized controlled trial of albumin rescue has not been performed.

The above experience demonstrates that a fundamental shift in burn resuscitation toward earlier use of colloids has been under way for years, ever since the first description of fluid creep and the complications that follow such overresuscitation.

PLASMA RECOGNIZED AS A TREATMENT FOR THE ENDOTHELIOPATHY OF TRAUMA

Meanwhile, a comprehensive reevaluation of fluid resuscitation strategies (crystalloid, blood component products, whole blood, etc.) in trauma patients has occurred over the past decade, energized by experience with combat casualties from the wars in Iraq and Afghanistan.[39] This effort began with "hemostatic resuscitation," which incorporated the early use of plasma, platelets, and RBCs in 1:1:1 ratios into the initial management of seriously injured patients.[40] Data have been published that support an independent coagulopathy of trauma as well as an endotheliopathy of trauma that is caused by hypoperfusion and ischemic injury to the endothelium.[41] These data supported the use of blood products to directly address the shock, coagulopathy, and endothelial injury that occur with life-threatening hemorrhage. Data on patients with blunt and penetrating trauma have increased interest in reanalyzing the effect of blood product–based resuscitation for severe burn injury because there are similarities in the microvasulature response to hypoperfusion.

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, etc.), to which glycosaminoglycans (heparan sulfate, hyaluronic acid, etc.) are attached. The glycoproteins act as adhesion molecules and include E- and P-selectins, integrins, and immunoglobulins, which participate in hemostasis and inflammation.[42] The glycocalyx not only forms a passive barrier between the blood and the endothelium, but also actively mediates the relationship between the two tissues. The glycocalyx is essential for maintaining an anticoagulant surface on the endothelium.[43] The glycocalyx "contains" a large volume (1–1.7 L) of noncirculating plasma within its meshwork.[44] It also serves as a "sensor," whereby information about fluid mechanical shear stress is transduced to the endothelial cell.[45] A description of how the glycocalyx participates in the control of transvascular fluid flux has been included in a revision of the Starling principle.[46,47]

Shedding of the glycocalyx may occur in response to ischemia/reperfusion, hypoxia, oxidative stress, hyperglycemia, hypervolemia, catecholamines, hemorrhagic shock, cardiac arrest, and sepsis.[42,48–52] Enzymes called "sheddases" mediate the degradation of the glycocalyx, to include matrix metalloproteinases, heparanases, hyaluronidases, and proteases.[52] Compounds that reportedly protect the glycocalyx include hydrocortisone, antithrombin III, protein C, nitric oxide, hyaluronic acid, albumin, N-acetylcysteine, plasma, and others.[44] Clinically, glycocalyx degradation is associated with shedding of the syndecan-1 ectodomain. Shed ectodomains following trauma are associated with enhanced shock, inflammation, and endothelial damage[53] and independently predict mortality in injured patients.[54]

A substantial body of evidence supports the concept that choice of fluids/perfusate influences microvascular permeability, and that this is mediated by the glycocalyx. Mason et al.[55] showed that perfusion of a frog mesenteric capillary with LR increased hydraulic conductivity by four to five times in comparison with plasma. This change was reversible by means of perfusion with bovine serum albumin, bovine gamma globulin, or human hemoglobin. In a similar model, Michel and Phillips[56] perfused single frog mesenteric capillaries with LR containing a macromolecule, Ficoll 70. They found that the addition of bovine serum albumin to the perfusate increased the effective osmotic pressure and reduced the hydraulic conductivity; the authors suggest that albumin may exert its effect on permeability by similar glycocalyx binding. Adamson and Clough[57] used cationized ferritin as a marker of the cell-surface glycocalyx. They perfused frog mesentery microvessels with cationized ferritin followed by frog plasma, bovine serum albumin, or LR. Using the bound ferritin as a biomarker, the glycocalyx thickness was twice as thick when perfused with plasma versus albumin or LR, supporting the clinical argument that plasma supports endothelial function.

Schneeberger and Hamelin[58] studied the effect of exchange perfusion with fluorocarbon emulsion in rats, which depletes circulating proteins. This procedure increased endothelial permeability to ferritin, along with loss of adsorbed albumin and IgG from the glycocalyx. Then, transfusion of serum protein–containing emulsion restored endothelial permeability. Lum and coauthors[59] studied the effects of albumin versus other

proteins on the transit of ^{125}I albumin across a pulmonary endothelial monolayer in vitro. Exposure of the cell culture to media alone led to an 83% increase in the ^{125}I albumin clearance rate. Repletion with 50% calf serum or with 2.0 g% albumin restored it to the control value. Other proteins tested (α1-acid glycoprotein, fibronectin) did not. Haraldsson and Rippe[60] used an isolated, perfused rat hindquarter preparation. Using pure dextran (no proteins) to perfuse the limbs induced a 45% increase in capillary filtration coefficient and a threefold increase of albumin clearance in the rat, a phenomenon called the "protein effect." However, they also found that serum proteins other than albumin were necessary to maintain normal albumin clearance rates, which they called the "serum effect." This provides evidence in support of the superiority of plasma to albumin for glycocalyx protection.

Kozar et al.[61] conducted studies of rats with hemorrhagic shock, then resuscitated with either LR or plasma. Shock caused degradation of the 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. Nelson and colleagues[62] 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. Torres Filho and colleagues[63] evaluated various resuscitation fluids in rats with 40% blood volume hemorrhage. Glycocalyx thickness (negatively) and microvascular permeability (positively) were correlated with plasma syndecan-1 and heparan 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. Pati and colleagues[64] 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 as well as 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.

Restoration of the glycocalyx is increasingly being recognized as an important therapeutic goal. Holcomb and colleagues[40,65] have demonstrated a decrease in mortality and improved outcomes in vitro and in vivo and clinically after trauma and hemorrhagic shock from plasma-based resuscitative strategies. 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.[66] Early plasma-based resuscitation reverses the endotheliopathy of trauma by restoring the glycocalyx. Using plasma rather than crystalloids as the primary volume expander has been associated with decreased morbidity and mortality in patients with hemorrhagic shock.[67] Joseph et al.[68] found in trauma laparotomy patients that minimizing the use of crystalloids was associated not only with improved outcomes but also virtually eliminated ACS. 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.[69]

In brief, there have been extensive studies in animal models and trauma patients that endorse the importance of the endothelial glycocalyx to include in the lungs[66] and the potential superiority of plasma to other fluids in protecting or restoring it following trauma/hemorrhage. Our central hypothesis is that the same problem of glycocalyx injury also pertains to burn shock and can be addressed with plasma-based resuscitation. Based on the aforementioned studies, there is a need to consider a paradigm shift for burn resuscitation and a move toward plasma-based resuscitation and away from the well-accepted crystalloid-based resuscitation strategy.

ENDOTHELIOPATHY OF BURNS

A recent study in rats with 25% or 40% TBSA burns demonstrated increased syndecan-1 shedding proportional to burn size; and that endothelial injury, manifested by leakage of albumin (Evan's blue dye) into the lungs, can be mitigated by the use of FFP.[70] In a prospective observational clinical study, and after adjusting for age, sex, TBSA, and inhalation injury, Osuka et al.[71] found that syndecan-1 shedding was independently correlated with increased fluid requirements and the development of burn-induced compartment syndromes. In addition to the recent findings of syndecan-1 shedding after burn injury, results of a large prospective study of burn patients by Stanojcic et al.[72] from March 2018 indicate a profound and substantial impact of burns greater than 40% TBSA on systemic morbidities. Interestingly, both IL-1β and IL-10 are associated with endothelial dysfunction and are modulated by plasma administration after hemorrhagic shock.[44] Additionally, TNFα is a known "Sdc1 sheddase" that is abrogated by plasma.[73] Both epinephrine and norepinephrine are mediators of the hypermetabolic response to burns and of endothelial cell dysfunction. Johansson et al.[54] have demonstrated that endogenous norepinephrine is independently associated with syndecan 1 and is a predictor of mortality after trauma, sepsis, and cardiac arrest. These previously unrecognized associations between burn-induced indices of systemic hyperinflammation and hypermetabolism and endothelial dysfunction suggest that plasma may have the potential to mitigate other sequelae of burn injury beyond edema. While there is overall a paucity of data in this area, we propose that there exists 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.

A significant knowledge gap exists concerning the utility of plasma in burn resuscitation in the modern era, but accumulating data suggest that it may be a fluid of choice. Du et al.[74] compared LR, FFP, and hypertonic saline for burn resuscitation almost 30 years ago. The volume infused was a mean of 4.8 mL/kg/TBSA in the LR group, 3.16 in the hypertonic saline group, and 2.68 in the FFP group. The median percent weight gain at the end of the first day of treatment was 10.7 in the LR group, 7.9 in the hypertonic saline group, and 2.4 in the FFP group. Their formula, incorporating FFP for resuscitation, is called the Slater formula.[9] While this study looked at burn edema, it did not look at more significant outcomes such as survival or intensive care unit length of stay. O'Mara and colleagues from the same group conducted a single-center randomized controlled trial of FFP (plus 2000 mL of LR) versus LR (at the Parkland dose) in 2004.[75] The FFP group demonstrated lower volume needs than the LR group (0.21 vs. 0.26 mL/kg) and virtually eliminated intra-abdominal hypertension. While this study favored plasma secondary to decreased risk of intra-abdominal hypertension, only 31 patients were included, and it was underpowered to identify any more than a trend. Plasma has in fact become incorporated into burn resuscitation at some burn centers despite there not being any high-quality prospective trials demonstrating improved outcomes; the above-mentioned International Society for Burn Injuries/American Burn Association survey stated that FFP was the preferred fluid for 13.9% of respondents.[37] However, there is no clear evidence that suggests plasma is the fluid of choice; large retrospective reviews and prospective trials are lacking. Given that there are different types of plasma products, some with better field expediency than others, plasma should be compared to standard crystalloid therapy, and if there are improved clinical outcomes, the different types of plasma (frozen, liquid, lyophilized) should be further investigated. Basic science data as well as data from the trauma community suggest that there is potentially beneficial biologic plausibility as well as a growing acceptance in the burn community concerning the use of plasma for early burn shock resuscitation; however, future trials are needed to evaluate the different resuscitation modalities to determine best practices in the burn patient population.

SUMMARY AND CONCLUSIONS

The risk of resuscitation morbidity in burn patients remains substantial with crystalloid-based resuscitation strategies. However, recent laboratory data support the use of plasma-based resuscitation, and there is growing acceptance in the burn community for plasma as an alternative to crystalloid resuscitation. Plasma for resuscitation is predicated on its ability to serve as a volume expander while protecting the endothelial glycocalyx in a variety of shock models to include burns. Research efforts should focus on prospective trials to evaluate the different forms of plasma compared to albumin and crystalloid resuscitation strategies. Comparative efficacy trials of plasma-based resuscitation are long overdue and should be conducted in burn patients.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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