Pathophysiology of severe burn injuries: new therapeutic opportunities from a systems perspective

Geoffrey P. Dobson*, PhD, FAHA, Jodie L. Morris, PhD
and Hayley L. Letson, PhD

Heart and Trauma Research Laboratory,
College of Medicine and Dentistry,
James Cook University, Queensland,
Australia, 4811

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To whom correspondence should be addressed.  Geoffrey P. Dobson, James Cook University, College of Medicine and Dentistry, 1 James Cook Drive, Townsville, Queensland, Australia, 4811. Email: geoffrey.dobson@jcu.edu.au Tel: +61 407-550235. Fax: 61-7-47 81 6279

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**Author contributions**

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To whom correspondence should be addressed:

Email: geoffrey.dobson@jcu.edu.au Phone: +61-407-550-235

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Abstract

Severe burn injury elicits a profound stress response with the potential for high morbidity and mortality. If polytrauma is present, patient outcomes appear to be worse. Sex-based comparisons indicate females have worse outcomes than males. There are few effective drug therapies to treat burn shock and secondary injury progression. The lack of effective drugs appears to arise from the current treat-as-you-go approach rather than a more integrated systems approach. In this review, we present a brief history of burns research and discuss its pathophysiology from a systems' perspective. The severe burn injury phenotype appears to develop from a rapid and relentless barrage of damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) and neural afferent signals, which leads to a state of hyperinflammation, immune dysfunction, coagulopathy, hypermetabolism and intense pain. We propose that if the central nervous system (CNS) control of cardiovascular function and endothelial-glycocalyx-mitochondrial coupling can be restored early, these secondary injury processes may be minimized. The therapeutic goal is to switch the injury phenotype to a healing phenotype by reducing fluid leak and maintaining tissue O$_2$ perfusion. Currently, no systems-based therapies exist to treat severe burns. We have been developing a small-volume fluid therapy comprising adenosine, lidocaine and magnesium (ALM) to treat hemorrhagic shock, traumatic brain injury and sepsis. Our early studies indicate that the ALM therapy holds some promise in supporting cardiovascular and pulmonary functions following severe burns. Future research will investigate the ability of ALM therapy to treat severe burns with polytrauma and sex disparities, and potential translation to humans.

Key words: ALM; adenosine, lidocaine, magnesium; trauma; military; pathophysiology; fluids; shock
Introduction

Severe burn injury elicits a profound stress response that appears to affect nearly every organ in the body. The purpose of this review is to discuss the pathophysiology of severe burns from a systems perspective. Before doing so, we will discuss the prevalence of burn trauma followed by a brief history of burn research and management. The major advances in treating burns have been largely driven by wars, terrorist attacks and great fires.

Modern burns: Framing the problem

Despite impressive advances, burns are still considered ‘the forgotten global health crisis’.

Kearney and colleagues (2018) \(^1\) p77

An underappreciated statistic is that the mortality rates from burn victims are similar to those for acute myocardial infarction \(^2\). Burns are the fourth most common trauma worldwide and affect more than 11 million people annually \(^3,4\). Over 90% of burn injuries occur in low- to middle-income countries, with Africa contributing ~66% of the total burden, followed by regions of the Eastern Mediterranean and South-East Asia \(^5,6\). The overall mortality from severe burns is ~5%, with most deaths being linked to hyperinflammation, immune compromise, multiple organ failure, infection and sepsis \(^7\). Poor outcomes are related to burn severity, advanced age, pre-existing comorbidities, and the presence of polytrauma \(^8\). Severe burn injuries are generally classified as \(\geq20\%\) total body surface area (TBSA) with >5% full thickness in adults, and \(\geq10\%\) TBSA in children (<10 years old) \(^4\).
Compared to civilians, military burn casualties are typically more severe with higher injury scores from polytrauma, infections and inhalation injuries\textsuperscript{3,9-13}.

Despite a decrease in mortality over past decades, the optimal treatment and resuscitative regimens have yet to be developed for the burn patient. This is particularly noteworthy when burns are accompanied by hemorrhage, or other trauma \textsuperscript{14-17}, and the effect of sex on these outcomes \textsuperscript{18,19}. A retrospective study involving 5061 adult burn patients in the Vietnam National Burn Hospital showed that females had a higher mortality after severe burns (>50% TBSA) compared to males \textsuperscript{19}. A more recent retrospective study involving 6431 patients from the WHO burn registry, showed that females had twofold higher in-hospital mortality than males in low- and middle-income countries \textsuperscript{18}. Similarly, higher mortality rates in women have been reported in higher income countries of the USA, Australia, and New Zealand \textsuperscript{18}. Reasons for why females appear more vulnerable to burn trauma require further investigation.

**Brief History: From the Battlefield to Civilian Medicine**

In every century, some sovereign remedies have appeared, which, after being more or less praised, have been replaced by others, and these, in their turn, have been forgotten.

Dupuytren, G (1832)\textsuperscript{20} p260-261
Five hundred years ago, some common remedies to treat burns included onion paste, excrement, oils, plant extracts, honey, vinegar, water, wine and alcohol. French military surgeon Ambroise Paré (c1510-1590) described a paste of fresh onions and salt to treat gunpowder burns that he found produced minimal blistering compared to traditional oils. In the late 1500s, German surgeon William Fabry (1560-1634) classified a burn into three degrees: 1) redness and blistering of skin; 2) withering of skin (without charring); and 3) eschar formation and charring. English surgeon Richard Wiseman (1622–1676) added depth of injury to Fabry’s classification, and later in 1743, German surgeon Lorenz Heister added time, and further conjectured that its underlying pathology was an inflammatory response. Scottish military surgeon John Hunter (1728-1793) also developed a heat treatment to reduce inflammation and pain. Others argued that cooling was the preferred treatment, a practice still used in today’s First Aid Guidelines. In addition to the degrees of burn classification, 19th century French military surgeon Guillaume Dupuytren (1777-1835) described the effect of severe burns on internal injuries which included gastric and intestinal ulcers, and a phenomenon at autopsy termed “intensive cerebral congestion” (see below). In the same century, despite the controversies regarding hot and cold or wet and dry applications to permit a scab to form, topical treatments and dressings became the mainstay, combined with new surgical techniques of excision, skin grafting, and aseptic procedures. In the 20th and 21st centuries, major advances and specialization in burn treatments were made from the developments in basic science, medicine and surgery. Over the past few decades, the spotlight on bacteriology and antibiotics, fluid resuscitation, wound excisions and scar management, have resulted in burn trauma mortality rates falling by over 50% compared to rates in the 1950s. Further advances in skin technologies and burn care management occurred from: 1) the Iraq and
Afghanistan wars, 2) increased terrorist attacks (e.g., 2002 Bali bombings), and 3) an increase in extreme fires around the world. Despite lower mortality rates, major knowledge gaps exist today, which we will now discuss from a systems perspective.

Pathophysiology of burns: inflammation and immune compromise

I believe no one will be offended at our treating of *Burns* as a Species of inflammation, since the appearance as well as the consequences of both are exactly the same .... When anything of this kind is applied to the body, the fibres and small vessels of the parts that are touched by it, will instantly corrugate and burn, whilst the blood and other contained fluids, will be extravasated, stagnate, and corrupt.

_Lorenz Heister (1739) 27 p220_

Immediately after a severe burn, a multitude of local and systemic injury responses are activated 3 (Table 1). Depending upon severity, the burn elicits an immediate stress response that manifests in two distinct phases; an acute burn shock (ebb) phase involving neurological, respiratory, cardiovascular, inflammatory, immune and musculoskeletal changes that may last days to months; followed by a hypermetabolic (flow) phase, which may last months to years 4,28,29. Even a 10% TBSA burn in adults can cause substantial pathological changes, albeit to a lesser extent than a severe burn 30. The main drivers of burn pathophysiology are hyperinflammation and immune dysfunction 31. Normally, inflammation and immune activation are beneficial and restorative 32,33. However, when they become hyperactivated in an uncontrolled manner after severe burns, they drive secondary injury progression, which is responsible for high morbidity and mortality 29.
Early 20th century observations equated poor outcomes in the burn patient to the presence of “burn toxins” originating from the wound. Today, the concept of “burn toxins” has been replaced with damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs) and other related immune modifying agents. The signals are released into the circulation from damaged or dying cells or from foreign pathogens, and together with the activation of neural afferent pathways, they trigger the central nervous system (CNS)-driven stress response (see below). The relentless barrage of DAMPs, PAMPs and neural signals are not mutually exclusive and may share co-receptors and accessory molecules that form “partnerships” to coordinate an immunoinflammatory response.

Although activation of this early response is exceedingly complex, a 2011 landmark study of Xiao and collaborators shed new light on the subject following burn injuries and blunt trauma. In the first 4-12 hours, the study showed there was 80% activation of the leukocyte transcriptome in the circulation, which lasted days to weeks. What predicted worse outcomes following burn trauma was not the magnitude of the genomic storm, but the time to resolve it. Another key finding of the study was that both pro- and anti-inflammatory pathways were activated early, challenging the traditional two-hit model, which proposes inflammation is activated first, and anti-inflammatory pathways second, to resolve it. Dysregulation and failure to resolve uncontrolled immunoinflammatory processes after severe burns can lead to immunosuppression, infection, sepsis, acute respiratory distress syndrome (ARDS) and multiple organ failure.

1. CNS stress response

Autopsy showed severe lesions in the whole nervous system, in the brain, and spinal marrow. The encephalic nervous system is then the seat of a violent irritation. Most of the phenomena of congestion and engorgement of nearly all the organs in the great cavities are seen.
Large surface burns are accompanied by an overwhelming CNS-driven stress response (Fig 2)\textsuperscript{3,4}. Nearly 200 years ago, Dupuytren, described at autopsy of young burn victims, a phenomenon termed “intensive cerebral congestion” or engorgement\textsuperscript{20}. The condition describes engorgement of the brain and its ventricles and the presence of ‘lacunes’ (small ischemic cerebral softenings)\textsuperscript{36}. In severely burned patients, congestion is also present in the lungs, heart and other organs\textsuperscript{20}. How a thermal injury at the periphery could affect the brain and internal organs located ‘in the great cavities’, remained a mystery for over a century. Today, as discussed above, these changes begin early and are driven by a myriad of incursions from DAMPs, PAMPs and immune cells that challenge the body’s multiple CNS-organ homeostatic circuits\textsuperscript{32,33}. At autopsy, recent data show that brain injury accounts for ~16% of all burn deaths, with 52% exhibiting cerebral edema with herniation, and 48% with anoxia\textsuperscript{37}, which implies a breach to the blood brain barrier (BBB) and loss of vascular integrity. Interestingly, ~25% of these burn patients had only minor burns\textsuperscript{36}, which underscores the importance of ‘silent’ secondary brain injury as an important clinical problem in burn patients, especially among children.

Burn-induced neurological complications are also linked to CNS-stress hormone discharge via the hypothalamic–pituitary–adrenal (HPA) axis\textsuperscript{38–41} and nucleus tractus solitarius (NTS)\textsuperscript{29,32}. Crum and colleagues reported in severe burn patients (30-60% TBSA) that plasma levels of epinephrine, norepinephrine, vasopressin, angiotensin II and neuropeptide Y were all elevated on hospital admission\textsuperscript{42}. Vasopressin levels, for example, were 50 times higher than normal, and did not return to normal ranges until days 4 or 5 post-admission\textsuperscript{42}. Despite an early sympathetic ‘stress’ discharge, less is known about regulation of the NTS following severe burns. NTS dysfunction is known to exacerbate hyperinflammation, immune
compromise, and multiple organ dysfunction via a number of feedback loops\textsuperscript{43,44}, including the CNS-cardiovascular, CNS-gut, CNS-spleen, and other circuits\textsuperscript{45}. The severe burn injury phenotype is complicated by the fact that whole body dysfunction can remain for several years or more after the initial injury\textsuperscript{46}.

2. Cardiac depression and dysfunction

Compromised cardiac function results in organ hypoperfusion, impaired peripheral microcirculation, burn zone extension, and reduced resistance to bacterial infection at the wound site.

Abu-Sittah and colleagues (2012)\textsuperscript{47} p26

The early sympathetic ‘stress’ discharge is also associated with early cardiovascular dysfunction after severe burns\textsuperscript{48}. As early as 15 minutes post-burn, cardiac output (CO) becomes depressed in the form of reduced contractility, slower isovolumic relaxation times and decreased left ventricular compliance\textsuperscript{47}. Cardiac depression can persist for hours to days, after which the body enters into a hyperdynamic state\textsuperscript{47}. The condition was first reported in the 1930s by Blalock and colleagues\textsuperscript{49}. A lower CO has been linked to many factors including: 1) a desensitization of the cardiac β-adrenergic receptors to higher neural and circulating catecholamine discharge, 2) lower venous return accompanying hypovolemia from fluid shifts and peripheral vasoconstriction, and 3) an ‘inhibitory factor’ that depresses cardiac metabolism via Ca\textsuperscript{2+} handling changes\textsuperscript{42,47,48,50-52}. With respect to an ‘inhibitory factor’, there is much controversy. Horton and colleagues reported the inflammatory
cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-1β secreted by cardiomyocytes followed a time course that was consistent with the early cardiac depression window. Kawai and colleagues further showed that ligating the mesenteric lymph duct in animal burn models improved cardiac function, suggesting ligation prevented some inhibitory factor from entering the circulation that subsequently depressed heart function. Cardiac dysfunction after burn injury has also been linked to changes in plasma and myocardial levels of macrophage migration inhibitor factor (MIF), a pluripotent proinflammatory cytokine, that is ubiquitously expressed in the heart and other organs.

Whatever factor (or factors) causes cardiac depression, it must be linked to changes in intracellular Ca²⁺ cycling that is responsible for contraction and relaxation. Elevated catecholamines, for example, can uncouple beta-adrenergic receptors from their G proteins, which in turn can lead to loss of pump function by increasing myocardial Ca²⁺ loading, apoptosis, cytokine production, nitric oxide (NO) upregulation, oxidative stress, and reduced mitochondrial function. In addition to putative circulating factors, other extra-cardiac factors could depress cardiac function, including changes to baroreceptor sensitivity, heart-rate variability, ventriculo-arterial coupling, systemic peripheral resistance, central venous pressure, and coronary vasoactive processes. In severe burn cases, cardiac dysfunction can often lead to burn shock that, if not treated immediately, is often fatal. Further studies are required to understand the nature, timing and mechanisms of cardiac dysfunction and shock after severe burns.
3. Loss of endothelial-glycocalyx integrity

Burn injury induces endothelial glycocalyx layer shedding similar to that in non-burn patients with endotheliopathy, and results in similar higher rate of mortality.

Welling and colleagues (2020) p386

Severe burn pathophysiology is synonymous with loss of vascular permeability and fluid loss. Fluid loss arises from a breach in the endothelial-glycocalyx that lines the inside of blood vessels. The endothelial-glycocalyx is a single cell layer that is normally anti-leak, anti-inflammatory, anti-adhesive, antithrombotic and anticoagulant that covers an enormous surface area in the body of ~55,000 m² (~200 tennis courts). The glycocalyx itself is the luminal facing, negatively charged, ‘fuzz-like’ mesh that is anchored to the single-layer endothelial cells. One can envisage that when the endothelial-glycocalyx becomes activated, the whole body becomes activated, and its phenotype changes. After a major burn, for example, the early sympathetic ‘stress’ discharge, cardiac depression and systemic hypoperfusion activates the endothelium causing it to shed its glycocalyx and become leaky, adhesive, proinflammatory, prothrombotic and vasoactive. Osuka and colleagues showed that the degree of glycocalyx shedding in burn patients was associated with increased fluid requirements. Of great clinical significance to severe burn patients, it appears that the glycocalyx can repair itself quickly under the right conditions. Currently, very little is known about the loss and recovery of the glycocalyx after severe burns. We hypothesize that restoring endothelial-glycocalyx integrity may reduce vascular leakage and hypovolemia, and improve O₂ delivery to tissue mitochondria, and presents a potential target for new therapeutics.
4. Hypermetabolism: Fueling the furnace and muscle wasting

Such a theory demands an exhaustion of the muscle by an excessive number of abnormal stimuli. This reflex wasting of muscle is undoubtedly responsible, in part, for the increased tissue catabolism.

Cuthbertson (1942) 28 p435

A metabolic stress response following severe burns was reported over 100 years ago 26,60. Cuthbertson attributed muscle wasting to an increase in trauma-induced tissue catabolism (above quote). It was not until the 1940s when Keyser conducted studies in burn patients that hypermetabolism began to be characterized 61. Today, it is a hallmark of severe burns and is associated with elevated body temperature, muscle lipolysis, glycogenolysis and proteolysis, and insulin-resistance 30, which, if not treated, leads to impaired wound healing, sepsis and multiorgan failure 60,62. From a clinical standpoint, current treatments to suppress metabolism include administration of recombinant human growth hormone, low-dose insulin infusion, use of synthetic testosterone analogue (oxandrolone), and beta blockade with propranolol 30,60,62. Unfortunately, treatments are only partially successful as the metabolic stress response may persist for a year or more after the initial injury 45.

Studies have shown that muscle oxygen consumption can increase ~2-fold from 64 to 130 mL/min after a severe burn (~50% TBSA) 2. The response is believed to be largely driven by the surge of catecholamines and glucocorticoids secondary to hyperinflammation and immune dysfunction 60.
Hypermetabolism also aggravates the immunoinflammatory response via release of immature myeloid cells from the spleen and implicates most, if not all, the body’s CNS-homeostatic circuits involving the brain, heart, adipose tissue, skeletal muscle, gut, liver and spleen (Fig. 2). A common denominator to the metabolic hyperdrive response appears to be mitochondrial dysfunction. Adipose tissue and skeletal muscle mitochondria, for example, become partly uncoupled and produce heat rather than ATP.

What are the underlying mechanisms of uncoupling following severe burn trauma? Although the mechanisms remain elusive, it likely involves changes to the transcriptional machinery that regulates mitochondrial oxidative metabolism and biogenesis. Some potential candidates that normally coordinate the metabolic supply and demand ratio include changes in expression of 5’ adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (Sirt-1), mitochondrially encoded cytochrome c oxidase III (MtCO3), and peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α). Differential expression of one or more of these master controllers may be responsible for the sustained hypermetabolic state in severe burn patients. New insights into the mechanisms may also come from winter hibernators or summer estivators that can switch their metabolic rate down to ‘pilot’ light then back again during arousal. Andrews showed the metabolic ‘switch’ appears to be linked to the gene expression of pyruvate dehydrogenase kinase isoenzyme 4, an enzyme that minimizes carbohydrate entry into the Krebs cycle. Others have suggested changes to the protein tyrosine phosphatases, which are known to switch metabolism “on/off” in a number of tissues, including neurones. Presumably, this putative ‘switch’ would be under CNS control involving the areas of the brain that control the release of stress hormones (see above). It is noteworthy that the hypothalamus controls energy metabolism, water balance, thermogenesis, circadian rhythms and sleep. To our knowledge, a molecular switch hypothesis of hypermetabolism in severe burn patients has not been investigated.
5. Gut barrier dysfunction: hypoperfusion exacerbates secondary injury

As part of their partnership in the symbiosis, the microbiota perform functions beneficial to the host, from enhancing digestion to protection from invasion of pathogens.

Goodrich et al (2017) 71 p 413

Another major component of the burn stress response is reduced gastrointestinal perfusion and subsequent changes to the gut-brain axis (Fig. 2) 72,73. This arises in part from the stress-related, sympathetically-controlled, constriction of the mesenteric artery that can lead to reduced perfusion by up to 60% 74-76. Gut wall ischemia, in turn, can lead to the translocation of bacteria and bacterial products into the blood and lymph, which can amplify vascular leak, immune dysfunction, inflammation, infectious complications, multiple organ dysfunction and sepsis 73,76. In addition, burn trauma can alter the composition of the gut microbiome 75. Earley and colleagues showed that in minor burn patients, Enterobacteriaceae in the gut accounted for less than 1% of the microbiome, and increased to 32% in severely burned patients 75. Given the importance of the gut microbiome to human health and immunoinflammatory function, it is possible that restoring it pre-burn composition may improve patient outcomes 73.

6. Coagulopathy: a poorly understood prothrombotic state with impaired fibrinolysis

In 3 patients with thermal burns the observations on fibrinolysis were repeated over a considerable period of time and it was noted that fibrinolysis which had been present during the period of shock disappeared after shock had been
Normal coagulation represents a fine balance between prothrombotic, anticoagulant and fibrinolytic pathways, which in turn depend on a healthy heart, intact endothelial-glycocalyx, circulating functioning platelets, and a highly regulated immunoinflammatory system. Trauma alters this balance in the blood in different ways. Burn-induced coagulation disorders were first noted in the 19th century, however, it was not until the early 20th century, when there was a greater understanding of blood clotting mechanisms, that new treatment strategies were possible. Understanding the mechanisms of fibrinolysis took longer. In 1946, Tagnon and colleagues were among the first to report fibrinolysis in burn shock patients, which they report was corrected after treatment. The group further argued that the precipitating cause of fibrinolysis was “a prolonged anoxic state,” which has subsequently been substantiated after prolonged major trauma.

Today, burn-induced coagulopathy is commonly characterized by early procoagulant changes, impaired fibrinolytic systems, and platelet dysfunction. Studies have shown burn coagulopathy is an independent predictor of 28-day mortality. By measuring plasma clotting times and fibrinogen levels, early procoagulant changes are often associated with a paradoxically decreasing fibrinogen, which illustrates the complexity of assessing and treating coagulopathy in burn patients.

Traditionally, this ‘paradox’ was believed to be disseminated intravascular coagulopathy (DIC), which is usually characterized by diffuse hemorrhage with consumption of fibrinogen, platelets and clotting factor VIII. However, DIC is rare and, by definition, must be accompanied by diffuse anatomopathologic fibrin position. Indeed, Barret and Gomez retrospectively analyzed 3331 consecutive burned patients and found that no deaths were attributed to DIC at autopsy. In very
extreme cases, McManus and colleagues reported five of 275 patients (1.8%) had “supranormal in vitro clotting” that may have been DIC syndrome based on biopsy small vessel fibrin thrombi coincident with septicemia and hypotension.

Part of the clinical problem of characterising coagulopathy in burn patients is that the older plasmatic clotting assays are unreliable. Newer viscoelastic methods (ROTEM and TEG) are superior because they provide real-time assessment of blood clotting functions and fibrinolysis. While it is generally accepted that the majority of severe burn patients are admitted to hospital in a hypercoagulable state, there is high variability that most likely reflects injury severity. In 2018, Huzar and colleagues performed TEG analysis on 65 burn patients (>15% TBSA) and reported that 60% of patients were hypercoagulable on admission and 24% were the opposite (i.e., hypocoagulable). In 2019, Wiegele and colleagues used ROTEM and thrombin generating assays on 20 consecutive severe burn patients (>20% TBSA) over a 2-week period and reported all were hypercoagulable on admission. Similar to other major trauma states, fibrinolytic variability in severe burn patients is also common. In a landmark study, Pusat and colleagues used TEG in 115 patients within 4 hours of thermal injury and found three admission fibrinolytic phenotypes; 1) high fibrinogen levels or fibrinolytic shutdown (SD); 2) normal fibrinogen levels or physiologic (PHYS) state; and 3) low fibrinogen levels or hyperfibrinolytic (HF) state. Sixty percent of burn patients presented with PHYS, 30% were SD, and 9% displayed the HF phenotype. Patients in the latter two categories had more severe burns (TBSA >20%). After adjustment for TBSA ≥20%, age, BMI, total Glasgow coma score (GCS) and inhalation injury, admission hyperfibrinolysis was associated with a nearly 13-fold higher risk of mortality and a five-fold shorter time to death compared to patients with normal fibrinogen (PHYS). High fibrinogen (SD) upon admission was not associated with increased mortality.
Collectively, these data illustrate again the complexity of early coagulopathy and fibrinolysis in burn patients, and the state of fibrinolysis. It is our hypothesis that the different clinical coagulopathy states with multiple fibrinolytic phenotypes reflect differences in vascular leakiness, endothelial activation and hypoperfusion. Improved CNS control of cardiovascular function to support tissue O₂ supply, we argue, will help to switch the burn injury phenotype to a healing one with improved outcomes, including reduced coagulopathy (see Future Directions below).

Fluid Therapies: Advances made from two theater and nightclub fires and war

None of the current proprietary resuscitation fluids have been formally evaluated for safety and efficacy.

Myburgh (2018) p862

Without adequate fluid resuscitation, severe burn patients are predisposed to develop hypovolemic shock, multiple organ dysfunction and possibly death [1,90]. Fluid therapy is therefore mandatory in adults (>15% TBSA) and critical in children (≥10% TBSA) [4]. Following a severe burn, plasma losses may exceed 4 ml per kilogram of body weight per hour [47,91]. The primary goal of fluid therapy is therefore to prevent vascular leakage and hypovolemia, and maintain adequate tissue perfusion and oxygenation (Fig 3) [80].
Fluid therapy became a mainstay for burn patients in the early-to-mid 20th century. A key proponent of fluid use was Yale’s Frank Underhill who in the 1930s stressed the need to correct hypovolemia and blood thickening. Underhill’s recommendations were based on his clinical experience with burn patients following the Rialto Theater fire (New Haven, Conn) in 1921 that killed nine and injured ~80 people. Patients received an IV saline infusion of 25 ml per minute supplemented by the drinking of water, and other treatments. Twenty years later, after another devastating fire at Cocoanut Grove nightclub (Boston, Mass), which killed nearly 500 people, Cope and Moore proposed a modification of the prevailing burn therapy to include the patient’s body weight and burn size. Cope and Moore also formulated an IV fluid solution that comprised 50% plasma and 50% saline. These two devastating fires represented a turning point in the history of the treatment of burn patients. The Second World War also led to wider fluid use for burn resuscitation, as well as new therapeutic blood product procedures.

Cope and Moore’s fluid therapy and administration protocol was the basis for the development of the Evans formula in 1952 and the Brooke formula a year later, which uses one-fourth plasma and three-fourths crystalloid. In 1968, Baxter and Shires removed plasma and developed their 100% crystalloid solution called the Parkland formula (also known as the Baxter Formula), which was administered as 4 ml x %TBSA x kg with the first half given in the first 8 hours, and the second half over the next 16 hours. Total fluid volume is important because aggressive fluid volumes may lead to the phenomenon of “fluid creep” that can exacerbate respiratory insufficiency, cardiac failure, inflammation, coagulopathy and compartment syndrome, the latter of which is associated with 80% mortality.
Different crystalloid compositions and vehicles have since been developed. Hypertonic saline is often used today to limit cellular edema and decrease the incidence of abdominal compartment syndrome \(^{95}\), whereas colloid adjuncts appear less popular, as they remain highly controversial \(^{4,10,93}\). Regardless of the type, timing and volume of fluid and method of administration, a number of issues with crystalloid solutions remain. An ongoing problem is the limited number of high quality, prospective, randomized controlled trials on the safety and efficacy of the different fluids, which may help explain the high variability of data in the trials that have been conducted \(^{89,91,96}\). Possible trial complications include patient recruitment heterogeneity, differences in fluid responsiveness \(^{97}\), and difficulty in selecting the appropriate endpoints that reflect improved tissue perfusion. Endpoints such as urine output >0.5 ml/kg per hour, base deficit <2, systolic blood pressure >90 mmHg and/or palpable pulse may not reflect adequate tissue perfusion (Fig 3) \(^3\). This is an important area of future research.

**Future Directions: Knowledge gaps and opportunities**

It is not sufficient to treat the wounded area only. Much more important is the recognition of systemic effects and the immediate institution of proper treatment to combat these effects.

Underhill, F.P. (1930) \(^{98}\) p842

Burn injury is a devastating trauma. If polytrauma is present, morbidity and mortality is greatly increased, and females appear more vulnerable than males \(^{14-17}\). *The lack of effective drug therapies to treat severe burn trauma we argue may be due to the current treat-as-you-go approach to*
research and practice, rather than a more integrated systems approach. Treating one symptom at a time can sometimes lead to what Shoemaker terms “contradictory therapeutic outcomes." The current single-nodal approach can be traced back to the molecular revolution of the 20th century, which began in earnest around 1953 after the discovery of DNA. Nobel Laureate Sir Francis Crick embodied this position when he wrote “the ultimate aim of the modern movement in biology is to explain all biology in terms of physics and chemistry.” The key point is that despite an overwhelming amount of mechanistic data has been generated at the molecular level from basic scientific research, its relevance to the workings of the whole body has not kept pace. Reductionism is important in breaking a complex system like burns into its simpler parts, but it does not do away with the system. New systems-based therapies are urgently required to restore the burn-induced defects that occur early in the multiple CNS-linked organ feedback circuits that drive secondary injury and poor outcomes.

What would a systems-based drug therapy look like? Ideally, a systems-based treatment would blunt the early CNS-driven stress response, promote CNS-cardiovascular coupling, protect the endothelial-glycocalyx, reduce inflammation, correct coagulopathy, and deliver sufficient O2 to mitochondria. No such drug exists. The clinical endpoints to test such a drug would be a significant reduction in vascular leakage and rapid restoration of tissue O2 perfusion. We have been developing an adenosine, lidocaine and magnesium (ALM) fluid therapy for non-compressible hemorrhagic shock, traumatic brain injury (TBI) and sepsis. The strategy being developed for far-forward battlefield and prehospital use, is to administer a small-volume 3% NaCl ALM IV bolus followed 60 min later by a 0.9% NaCl ALM drip infusion for 4 hours. We have shown in rat and pig hemorrhagic shock models that ALM therapy increases mean arterial pressure (MAP) from shock values (~30-40 mmHg) into the permissive hypotensive range (MAP ~60 mmHg), while providing
neuroprotection and reducing secondary injury\textsuperscript{80,103,104}. We have used this data to formulate a Systems Hypothesis of Trauma (SHOT), which may also be applicable for severe burns\textsuperscript{44,80}.

Lastly, we recently completed a pilot study in the rat model of 30\% TBSA severe scald burn and found that small-volume ALM therapy: 1) protected the lung by reducing oxidative stress indicated by a significant 75\% fall in malondialdehyde levels, 2) maintained alveolar and epithelial integrity, and 3) improved cardiac function and O\textsubscript{2} delivery in the first 8 hours\textsuperscript{105}. Currently, we are working on optimal ALM dosages for severe burn injury, with and without hemorrhage, compared to standard-of-care Lactated Ringers. If successful, the therapy may provide a new therapy for burn trauma.

**Conclusions**

Severe burn trauma induces a major CNS-driven stress response that affects almost every organ in the body. After the initial burn, the injury phenotype is maintained by a rapid and relentless barrage of DAMPs and PAMPs signals, which leads to hyperinflammation, immune dysfunction, endotheliopathy, coagulopathy, hypermetabolism, and multiple organ dysfunction. New systems-acting drugs are required to switch the burn injury phenotype to a burn restorative phenotype by increasing CNS-cardiovascular coupling, reducing microvascular leakage, and restoring adequate tissue perfusion which, we believe, will reduce secondary injury and improve outcomes. We are developing a systems-based, small-volume ALM fluid therapy that may be useful in the early treatment of severe burn patients.
References


103. Letson HL, Dobson GP. 3.0% NaCl Adenosine, lidocaine, Mg2+ (ALM) bolus and 4 hours ‘drip’ infusion reduces non-compressible hemorrhage by 60% in a rat model. *J Trauma Acute Care Surg.* 2017;82(6):1063-1072.


Figure Legends

**Figure 1.**

Brief history of the main events of burn trauma from the 1500s to the present. Most major advances in emergency care and clinical management have been driven by wars and great fires (see text).

**Figure 2.**

Schematic of the systems’ effect of severe burn trauma on the CNS and organs of the body. New drug therapies are required break these CNS-driven injury cycles that lead to poor outcomes and treat the system, not single nodal targets that treat one symptom after another as they occur in the burn patient (see text). New therapies are required to break these CNS-driven injury cycles that lead to poor outcomes. CNS, central nervous system; TBSA, total body surface area; DAMP, damage-associated molecular pattern; PAMP, pathogen-associated molecular pattern.

**Figure 3.**

Selecting the optimal intravenous (IV) fluid composition, volume and timing to treat severe burn patients remains challenging. Decisions should be based on clinical assessment of the patient’s individual needs and cardiac responsiveness to fluids. Delivering a fluid too little, too much or too early, in hypovolemic burn patients can do more harm than good. There is a clear need for consensus guidance on the selection and administration of IV fluid therapy to accurately improve tissue perfusion and restore sufficient O₂ supply to tissue mitochondria after severe burn injury to prevent end-organ dysfunction and poor outcomes. CNS, central nervous system; ADP, adenosine diphosphate; ATP, adenosine triphosphate.
Table 1 Severe burn trauma involves at least seven overlapping stages of secondary injury progression driven by inflammation and immune dysfunction.

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<table>
<thead>
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<tbody>
<tr>
<td>1</td>
<td>CNS stress response</td>
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<tr>
<td>2</td>
<td>Cardiac depression and dysfunction</td>
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<tr>
<td>3</td>
<td>Loss of endothelial-glycocalyx integrity</td>
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<td>4</td>
<td>Hypermetabolism</td>
</tr>
<tr>
<td>5</td>
<td>Gut barrier dysfunction</td>
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<td>6</td>
<td>Coagulopathy</td>
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<tr>
<td>7</td>
<td>Multiple-organ dysfunction</td>
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</tbody>
</table>
Figure 1

Brief History of Military and Civilian Burn Trauma

2022 Advancements in skin grafting, dressings, tissue-engineered substitutes and immunomodulated bioactive dressings.

2003 Finkel and colleagues introduced the concept of burn severity based on total body surface area.

2005-2010 Jochims and colleagues report that secondary injury can persist for at least 5-10 years.

1993 Frimpong and colleagues showed immunosuppression, fibrosis, and mortality in severely burned patients.

1983 Evans and colleagues provided a synthesis of fluid and electrolyte requirements for severe burns patients.

1981 Wallace, Piantini and Terzis proposed a simplified "Rule of Nine" method to assess burn TBSA. Methods have improved to include age and a prognostic value which predicted death.

1980s Cope and Macrae also formulated an IV fluid solution that comprised 50% plasma and 50% saline.

World War II saw developments in medical evacuation for burns and antibiotics to prevent infection. Toxins were developed for discriminating 2nd and 3rd degree burns. Major advances were made in plastic surgery.

1932 Frank Underhill (1877-1932) proposed a better understanding of burn pathophysiology and showed that burn shock correlated with increased hematocrit, secondary to fluid and electrolyte loss. Underhill stressed correcting plasma volume with fluids and early burn.

1925-26 Du Bois and Platt independently provided formulas to calculate body surface area when height and weight are known.

Early 20th century Burn treatment involved mechanical cleansing, surgical debridement and topical solutions to prevent the stenosis of "source from the burn wound and to dry out the wound to allow formation of hard escharum to minimize fluid loss.

1917-1918 Following the early work of Gerhard von Swentzel (1776) and Voel-Boll (1803), saline infusions for severe burns were performed locally.

1669 French surgeon Jacques Louis Alphonse (1662-1730) perfomed one of the first "deep" skin graft procedures under anesthesia in Denmark.

1697 British surgeon Joseph Lister (1827-1912) adopted Pasteur's germ theory and pioneered antiseptic procedures. Lister postulated that infection came from exposure of the wound to the air in the absence of the protection of the skin. Treated the anthrax poisoning of Pasteur and Pasteur.

1666 French physician H. Deslandes (1480-1529) described the formation and destruction of blood vessels after a burn and observed that diffusion was slower in narrow vessels.

1659 Claude Bernard (1912-1879) formulated his theory of the "laws of the circulation" to preserve the human condition of the internal environment, and to ensure the CNS.

1645 The first hospital for the treatment of large burns was established on the grounds of the Edinburgh Royal Infirmary.

1632 Guillaume Dupuytren reported gastric and intestinal dysfunction in burn patients, and first described "injury of the bowel in burns victims.

Before the 17th century: Investigations demonstrated that, after a burn, fluid is lost from the blood and the blood became thinner. Immediate cooling was controversial.

1823 German surgeon Johann Friedrich Dippel (1702-1845) studied skin grafting but apparently was unsuccessful in performing a first graft in humans.

1799 Surgeon James Bart (1755-1815) advocated immediate cooling of the burn wound to halt injury progression, which is a part of the first aid recommended today.

1777 Edward Jenner's Essay on Burns described pressure dressing burns to relieve pain and reduce healing.

1764 Battlefield Surgeon and physician John Hunter (1728-1793) published his famous A Treatise on the Burn, Inflammation and Gangrenous Wounds. He believed burn treatment was a treatment of trauma and inflammation and avoiding the burn was not preventative.

1640s English surgeon William Fotherby (1640-1844) wrote a burn treatise On the Burning and classified a burns into five degrees and described a windlass (hanging stock).

1526 English surgeon William Cower (1516-1609) advanced the application of purgatives and stimulants, e.g. enemias and ointments, for purgative burns.

1457 French surgeon Armand Paré (c.1510-1590) pioneered new surgical techniques for battlefield medicine, especially wound healing.

War and burn war is more than just a battle to know its importance in burn trauma, and how not to medically and surgically on the battlefield.
Figure 2

Systems-approach to severe burn trauma

Females have higher mortality than males after severe burns

Secondary Injury
- Vascular leak
- Hypoperfusion
- Endotheliopathy
- Hypermetabolism
- Mitochondrial dysfunction
- Inflammation
- Immune dysfunction
- Coagulopathy

CNS Stress Response
- Catecholamine surge

Drivers of secondary injury include DAMPs, PAMPs, cytokines, chemokines, immune cells, complement, neural modulators and immune-modifying agents (see text)
Figure 3

Goals of fluid resuscitation in burn patients

Too Little Fluid
- Hypotension
- Tissue hypoperfusion
- Hypovolemic shock
- Dehydration
- Mitochondrial dysfunction
- Multiple organ dysfunction
- Inflammation
- Coagulopathy
- CNS dysfunction

Sex differences?

OPTIMAL CLINICAL ENDPOINTS
- \( \uparrow \) CNS-cardiovascular coupling
- \( \downarrow \) Hypovolemia
- \( \downarrow \) Vascular leakiness
- \( \uparrow \) Increase tissue perfusion
- \( \uparrow \) \( O_2 \) supply to mitochondria

Return of Steady-State
- \( \downarrow \) Hypoperfusion
- \( \downarrow \) Ischemia
- \( \downarrow \) Hypoxia

ADP \( \uparrow \) ATP

Regardless of the type, timing and volume of resuscitation fluid, there have been few formal clinical studies comparing the different safety and efficacy profiles of the different fluids used for burn trauma in civilian and military environments.