

# Pathophysiology of Severe Burn Injuries: New Therapeutic Opportunities From a Systems Perspective

Geoffrey P. Dobson, PhD, FAHA<sup>\*,</sup>; Jodie L. Morris, PhD<sup>\*,</sup>; Hayley L. Letson, PhD<sup>\*</sup>

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, pathogen-associated molecular patterns, 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 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<sub>2</sub> 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 et al (2018)<sup>1</sup> (p<sup>77</sup>)

An underappreciated statistic is that the mortality rates from burn victims are similar to those for acute myocardial infarction.<sup>2</sup> Burns are the fourth most common trauma worldwide and affect more than 11 million people annually.<sup>3,4</sup> 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.<sup>5,6</sup> The overall mortality from severe burns is ~5%, with most deaths being linked to hyperinflammation, immune compromise, multiple-organ failure, infection, and sepsis.<sup>7</sup> Poor outcomes are related to burn severity, advanced age, preexisting comorbidities, and the presence of polytrauma.<sup>8</sup> Severe burn injuries are generally classified as ≥20% TBSA, with >5% full thickness in adults, and ≥10% TBSA in children (<10 years old).<sup>4</sup> Compared to civilians, military burn casualties are typically more severe with higher injury scores from polytrauma, infections, and inhalation injuries.<sup>3,9-13</sup>

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,<sup>14-17</sup> and the effect of sex on these outcomes.<sup>18,19</sup> A

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

**Author Contributions:** Geoffrey Phillip Dobson (Conceptualization [lead], Formal analysis [equal], Funding acquisition [equal], Methodology [lead], Supervision [lead], Writing—original draft [lead], Writing—review & editing [equal]), Jodie Louise Morris (Conceptualization [equal], Formal analysis [equal], Resources [equal], Writing—original draft: Supporting; Writing—review & editing [supporting]), and Hayley Louise Letson (Conceptualization [equal], Funding acquisition [equal], Methodology [equal], Software [lead], Writing—original draft [equal], Writing—review & editing [equal])

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\*Address correspondence to G.P.D. (email: [geoffrey.dobson@jcu.edu.au](mailto:geoffrey.dobson@jcu.edu.au))

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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.<sup>19</sup> A more recent retrospective study involving 6431 patients from the WHO burn registry showed that females had 2-fold higher in-hospital mortality than males in low- and middle-income countries.<sup>18</sup> Similarly, higher mortality rates in women have been reported in higher income countries such as United States, Australia, and New Zealand.<sup>18</sup> Reasons for why females appear more vulnerable to burn trauma require further investigation.

### Brief history: from the battlefield to civilian medicine

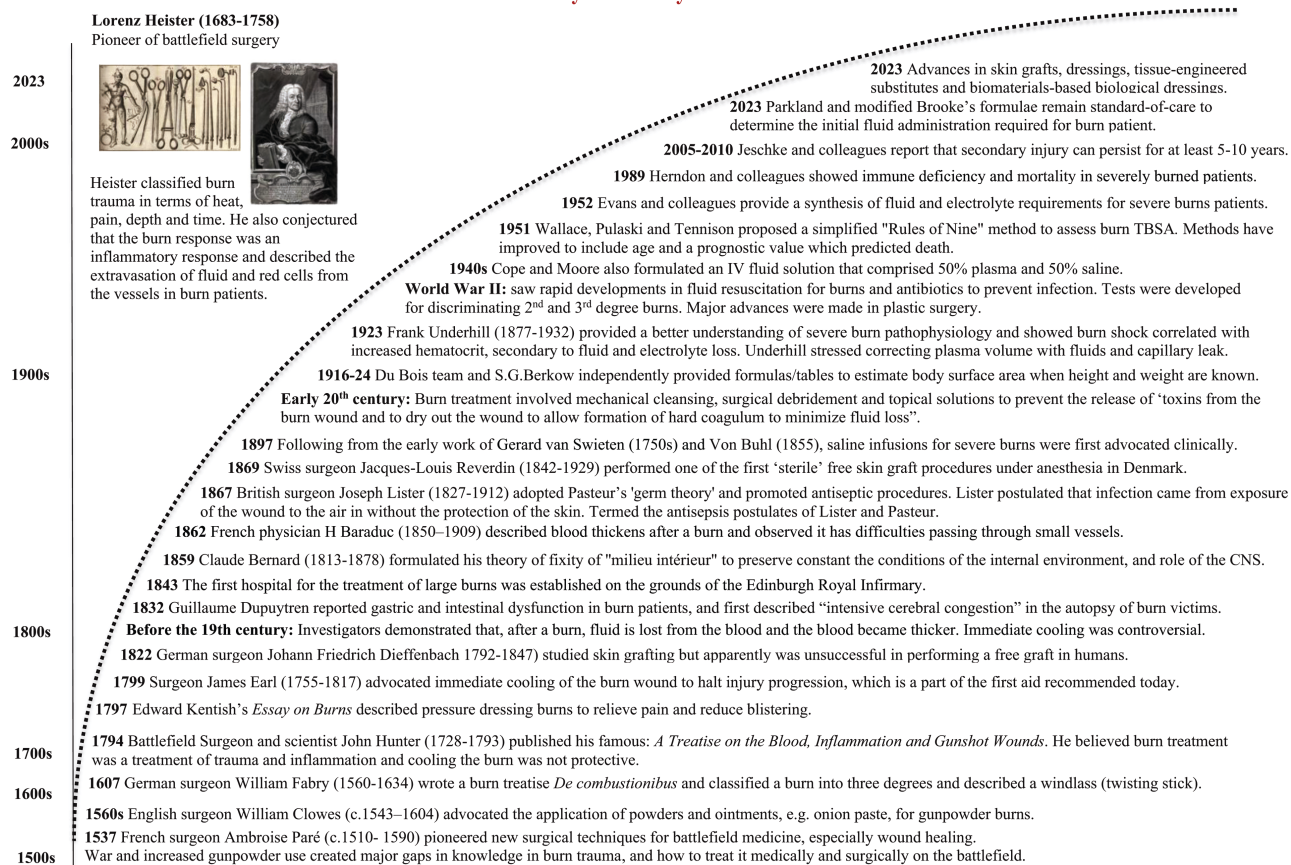
*In every century, some sovereign remedies have appeared, which, after being more or less praised, have been replaced by others, and these, in their turn, have been forgotten.*

Dupuytren, G (1832)<sup>20(p260-261)</sup>

Five hundred years ago, some common remedies to treat burns included onion paste, excrement, oils, plant extracts, honey, vinegar, water, wine, and alcohol.<sup>21,22</sup> 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 (Figure 1).<sup>23</sup> In the late 1500s, German surgeon William Fabry (1560-1634) classified a burn into 3 degrees: (1) redness and blistering of skin; (2) withering of skin (without charring); and (3) eschar formation and charring<sup>24</sup> (Figure 1). English surgeon Richard Wiseman (1622-1676) added depth of injury to Fabry's classification,<sup>24</sup> and later in 1743, German surgeon Lorenz Heister added time and further conjectured that its underlying pathology was an inflammatory response (see Heister's quote below). 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 (Figure 1),<sup>25</sup> 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,<sup>25</sup> topical treatments and dressings became the mainstay, combined with new surgical techniques of excision, skin grafting, and aseptic procedures (Figure 1). Specialized wards in hospitals grew in number, largely the result of nonburn patients complaining about the horrific sites they were witnessing during their stay.

### Brief History of Military and Civilian Burn Trauma



**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)

In the 20th and 21st centuries, major advances and specialization in burn treatments were made from the developments in basic science, medicine, and surgery.<sup>1,26</sup> 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.<sup>1</sup> Further advances in skin technologies and burn care management occurred from (1) the Iraq and Afghanistan wars, (2) increased terrorist attacks (eg, 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)<sup>27(p220)</sup>

Immediately after a severe burn, a multitude of local and systemic injury responses are activated<sup>3</sup> (Table 1). Depending on severity, the burn elicits an immediate stress response that manifests in 2 distinct phases: an acute burn shock 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.<sup>4,28,29</sup> Even a 10% TBSA burn in adults can cause substantial pathological changes, albeit to a lesser extent than a severe burn.<sup>30</sup> The main drivers of burn pathophysiology are hyperinflammation and immune dysfunction.<sup>31</sup> Normally, inflammation and immune activation are beneficial and restorative.<sup>32,33</sup> 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.<sup>29</sup>

Early 20th-century observations equated poor outcomes in the burn patient to the presence of “burn toxins” originating from the wound.<sup>34</sup> 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.<sup>29,32</sup> 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).<sup>29,32,33</sup> *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.*<sup>32,33</sup>

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.<sup>35</sup> 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.<sup>33</sup> *What predicted worse outcomes following burn trauma was not the magnitude of the genomic storm, but the time to resolve it.*<sup>35</sup> Another key finding of the study was that both pro- and anti-inflammatory pathways were activated early, challenging the traditional 2-hit model, which proposes that inflammation is activated first, and anti-inflammatory pathways second, to resolve it.<sup>33,35</sup> Dysregulation and failure to resolve uncontrolled immunoinflammatory processes after severe burns can lead to immunosuppression, infection, sepsis, acute respiratory distress syndrome, and multiple-organ failure.<sup>31</sup>

## 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.*

Guillaume Dupuytren (1832)<sup>20(p239)</sup>

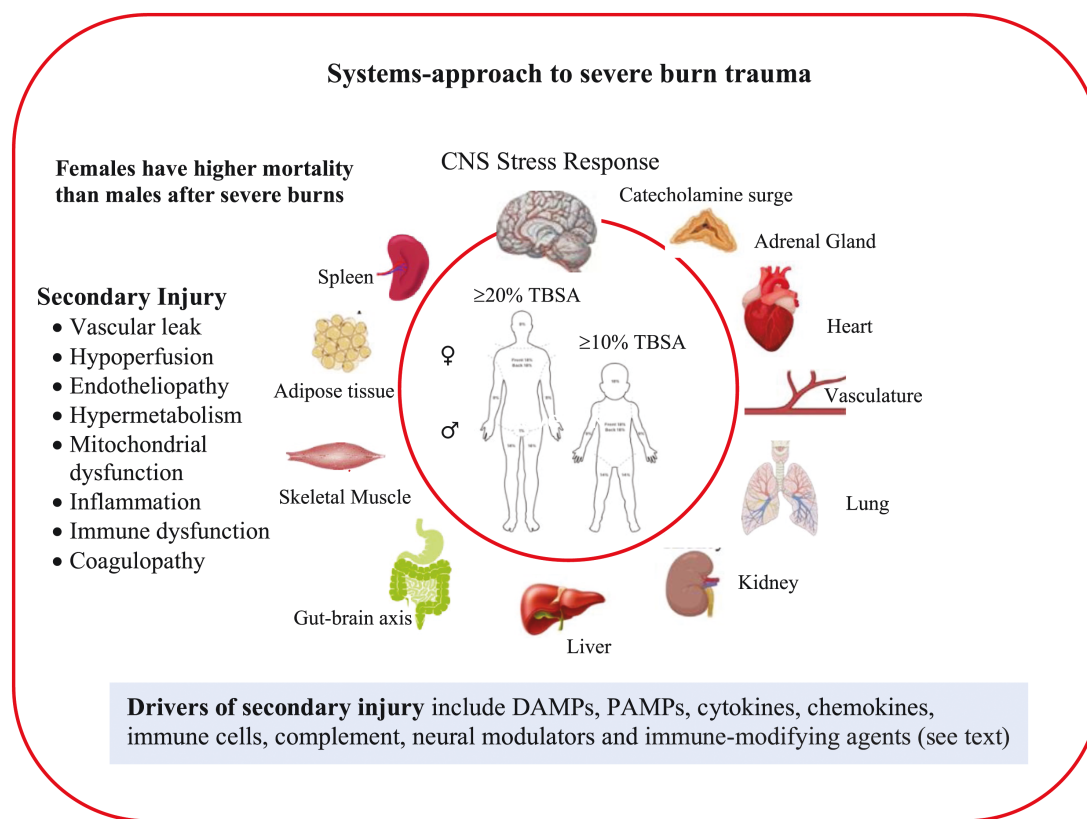
Large surface burns are accompanied by an overwhelming CNS-driven stress response (Figure 2).<sup>3,4</sup> Nearly 200 years ago, Dupuytren described at autopsy of young burn victims, a phenomenon termed “intensive cerebral congestion” or engorgement.<sup>20</sup> The condition describes engorgement of the brain and its ventricles and the presence of “lacunes” (small ischemic cerebral softenings).<sup>36</sup> In severely burned patients, congestion is also present in the lungs, heart, and other organs.<sup>20</sup> How a thermal injury at the periphery that 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.<sup>32,33</sup> 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,<sup>37</sup> which implies a breach to the blood brain barrier and loss of vascular integrity. Interestingly, ~25% of these burn patients had only minor burns,<sup>36</sup> 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 axis<sup>38–41</sup> and nucleus tractus solitarius (NTS).<sup>29,32</sup> Crum et al reported in severe burn patients

**Table 1.** Severe Burn Trauma Involves At Least 7 Overlapping Stages of Secondary Injury Progression Driven by Inflammation and Immune Dysfunction

1. CNS stress response
2. Cardiac depression and dysfunction
3. Loss of endothelial-glycocalyx integrity
4. Hypermetabolism
5. Gut barrier dysfunction
6. Coagulopathy
7. Multiple-organ dysfunction





**Figure 2.** Schematic of the Systems' Effect of Severe Burn Trauma on the CNS and Organs of the Body. New Drug Therapies Are Required to 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). CNS, Central Nervous System; DAMP, Damage-Associated Molecular Pattern; PAMP, Pathogen-Associated Molecular Pattern; TBSA, Total Body Surface Area

(30%-60% TBSA) that plasma levels of epinephrine, norepinephrine, vasopressin, angiotensin II, and neuropeptide Y were all elevated on hospital admission.<sup>42</sup> Vasopressin levels, for example, were 50 times higher than normal and did not return to normal ranges until days 4 or 5 postadmission.<sup>42</sup> 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,<sup>43,44</sup> including the CNS–cardiovascular, CNS–gut, CNS–spleen, and other circuits.<sup>45</sup> 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.<sup>46</sup>

#### 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 et al (2012)<sup>47</sup> (p26)*

The early sympathetic “stress” discharge is also associated with early cardiovascular dysfunction after severe burns.<sup>48</sup> As early as 15 minutes postburn, cardiac output (CO) becomes

depressed in the form of reduced contractility, slower isovolumic relaxation times, and decreased left ventricular compliance.<sup>47</sup> Cardiac depression can persist for hours to days, after which the body enters into a hyperdynamic state.<sup>47</sup> The condition was first reported in the 1930s by Blalcock et al.<sup>49</sup> A lower CO has been linked to many factors including (1) a desensitization of the cardiac  $\beta$ -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  $\text{Ca}^{2+}$  handling changes.<sup>42,47,48,50–52</sup> With respect to an “inhibitory factor,” there is much controversy. Horton et al reported the inflammatory cytokines tumor necrosis factor- $\alpha$  and interleukin (IL)-1 $\beta$  secreted by cardiomyocytes followed a time course that was consistent with the early cardiac depression window.<sup>53</sup> Kawai et al 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.<sup>54</sup> Cardiac dysfunction after burn injury has also been linked to changes in plasma and myocardial levels of macrophage migration inhibitor factor, a pluripotent proinflammatory cytokine, that is ubiquitously expressed in the heart and other organs.<sup>55</sup>



Whatever factor (or factors) causes cardiac depression, it must be linked to changes in intracellular  $\text{Ca}^{2+}$  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  $\text{Ca}^{2+}$  loading, apoptosis, cytokine production, nitric oxide upregulation, oxidative stress, and reduced mitochondrial function.<sup>47,52,53</sup> In addition to putative circulating factors, other extracardiac factors could depress cardiac function, including changes to baroreceptor sensitivity, heart-rate variability, ventriculoarterial coupling, systemic peripheral resistance, central venous pressure, and coronary vasoactive processes.<sup>33,44,48</sup> In severe burn cases, cardiac dysfunction can often lead to burn shock that, if not treated immediately, is often fatal (see Fluid therapies).<sup>56</sup> Further studies are required to understand the nature, timing, and mechanisms of cardiac dysfunction and shock after severe burns.

#### *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 et al (2020)<sup>57</sup> (p386)

Severe burn pathophysiology is synonymous with loss of vascular permeability and fluid loss.<sup>13,33,57</sup> Fluid loss arises from a breach in the endothelial-glycocalyx that lines the inside of blood vessels.<sup>13,57</sup> 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  $\sim 55,000 \text{ m}^2$  ( $\sim 200$  tennis courts).<sup>33</sup> The glycocalyx itself is the luminal facing, negatively charged, “fuzz-like” mesh that is anchored to the single-layer endothelial cells.<sup>13,57</sup> *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.<sup>33</sup> Osuka et al showed that the degree of glycocalyx shedding in burn patients was associated with increased fluid requirements.<sup>58</sup> Of great clinical significance to severe burn patients, it appears that the glycocalyx can repair itself quickly under the right conditions.<sup>59</sup> Currently, very little is known about the loss and recovery of the glycocalyx after severe burns.<sup>57</sup> We hypothesize that restoring endothelial-glycocalyx integrity may reduce vascular leakage and hypovolemia, and improve  $\text{O}_2$  delivery to tissue mitochondria, and present a potential target for new therapeutics.

#### *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)<sup>28</sup> (p435)

A metabolic stress response following severe burns was reported over 100 years ago.<sup>26,60</sup> 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.<sup>61</sup> Today, it is a hallmark of severe burns and is associated with elevated body temperature, muscle lipolysis, glycogenolysis and proteolysis, and insulin resistance,<sup>30</sup> which, if not treated, leads to impaired wound healing, sepsis, and multiorgan failure.<sup>60,62</sup> From a clinical standpoint, current treatments to suppress metabolism include administration of recombinant human growth hormone, low-dose insulin infusion, use of synthetic testosterone analog (oxandrolone), and  $\beta$  blockade with propranolol.<sup>30,60,62</sup> Unfortunately, treatments are only partially successful as the metabolic stress response may persist for a year or more after the initial injury.<sup>45</sup>

Studies have shown that muscle oxygen consumption can increase  $\sim 2$ -fold from 64 to 130 mL/min after a severe burn ( $\sim 50\%$  TBSA).<sup>2</sup> The response is believed to be largely driven by the surge of catecholamines and glucocorticoids secondary to hyperinflammation and immune dysfunction.<sup>60</sup> Hypermetabolism also aggravates the immunoinflammatory response via release of immature myeloid cells from the spleen<sup>45</sup> and implicates most, if not all, of the body's CNS-homeostatic circuits involving the brain, heart, adipose tissue, skeletal muscle, gut, liver, and spleen (Figure 2).<sup>30,45,62</sup> 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.<sup>2</sup>

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.<sup>63,64</sup> Some potential candidates that normally coordinate the metabolic supply and demand ratio include changes in expression of 5' adenosine monophosphate-activated protein kinase, sirtuin-1, mitochondrially encoded cytochrome c oxidase III, and peroxisome proliferator-activated receptor-gamma coactivator-1alpha.<sup>65</sup> 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.<sup>66</sup> 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.<sup>67</sup> Others have suggested changes to the protein tyrosine phosphatases, which are known to switch metabolism “on/off” in a number of tissues, including neurones.<sup>68</sup> Presumably, this putative “switch” would be under CNS control involving the areas of the brain that control the release of stress hormones (see above).<sup>69</sup> It is noteworthy that the hypothalamus controls energy metabolism, water balance, thermogenesis, circadian rhythms, and sleep.<sup>70</sup> To our knowledge, a molecular switch hypothesis of hypermetabolism in severe burn patients has not been investigated.

*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)<sup>71(p413)</sup>

Another major component of the burn stress response is reduced gastrointestinal perfusion and subsequent changes to the gut–brain axis (Figure 2).<sup>72,73</sup> 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%.<sup>74–76</sup> 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.<sup>73,76</sup> In addition, burn trauma can alter the composition of the gut microbiome.<sup>75</sup> Earley et al 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.<sup>75</sup> 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.<sup>73</sup>

*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 effectively treated.*

Tagnon et al (1946)<sup>77(p94)</sup>

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.<sup>78</sup> Trauma alters this balance in the blood in different ways.<sup>78,79</sup> 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.<sup>10</sup> Understanding the mechanisms of fibrinolysis took longer. In 1946, Tagnon et al were among the first to report fibrinolysis in burn shock patients, which they report was corrected after treatment.<sup>77</sup> The group further argued that the precipitating cause of fibrinolysis was “a prolonged anoxic state,”<sup>77</sup> which has subsequently been substantiated after prolonged major trauma.<sup>80</sup>

Today, burn-induced coagulopathy is commonly characterized by early procoagulant changes, impaired fibrinolytic systems, and platelet dysfunction.<sup>81–83</sup> Studies have shown burn coagulopathy is an independent predictor of 28-day mortality.<sup>81–83</sup> 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),<sup>78,84</sup> which is usually characterized by diffuse hemorrhage with consumption of fibrinogen, platelets, and clotting factor VIII.<sup>85</sup> However, DIC is rare and, by definition, *must be accompanied by diffuse anatomopathologic fibrin position.*<sup>78,79</sup> Indeed, Barret and Gomez retrospectively analyzed 3331 consecutive burned patients and found that no deaths were attributed to DIC at autopsy.<sup>84</sup> In very extreme cases, McManus et al reported that 5 of 275 patients (1.8%) had “supranormal in vitro clotting” that may have DIC syndrome based on biopsy of small vessel fibrin thrombi coincident with septicemia and hypotension.<sup>85</sup>

Part of the clinical problem of characterizing coagulopathy in burn patients is that the older plasmatic clotting assays are unreliable.<sup>78,86</sup> Newer viscoelastic methods (ROTEM and TEG) are superior because they provide real-time assessment of blood clotting functions and fibrinolysis.<sup>79</sup> *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 et al performed TEG analysis on 65 burn patients (>15% TBSA) and reported that 60% of patients were hypercoagulable on admission and 24% were the opposite (ie, hypocoagulable).<sup>87</sup> In 2019, Wiegeler et al 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.<sup>86</sup> Similar to other major trauma states, fibrinolytic variability in severe burn patients is also common. In a landmark study, Pusateri et al used TEG in 115 patients within 4 hours of thermal injury and found 3 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.<sup>88</sup> Sixty percent of burn patients presented with PHYS, 30% were SD, and 9% displayed the HF phenotype. Patients in the latter 2 categories had more severe burns (TBSA > 20%). After adjustment for TBSA ≥ 20%, age, BMI, total Glasgow Coma Score, and inhalation injury, admission hyperfibrinolysis was associated with a nearly 13-fold higher risk of mortality and a 5-fold shorter time to death compared to patients with normal fibrinogen (PHYS). High fibrinogen (SD) on admission was not associated with increased mortality.<sup>88</sup>

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 O<sub>2</sub> supply, we argue, will help to switch the burn injury phenotype to a healing one with improved outcomes, including reduced coagulopathy (see Future directions).

*Fluid therapies: advances made from 2 theater and nightclub fires and war*

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

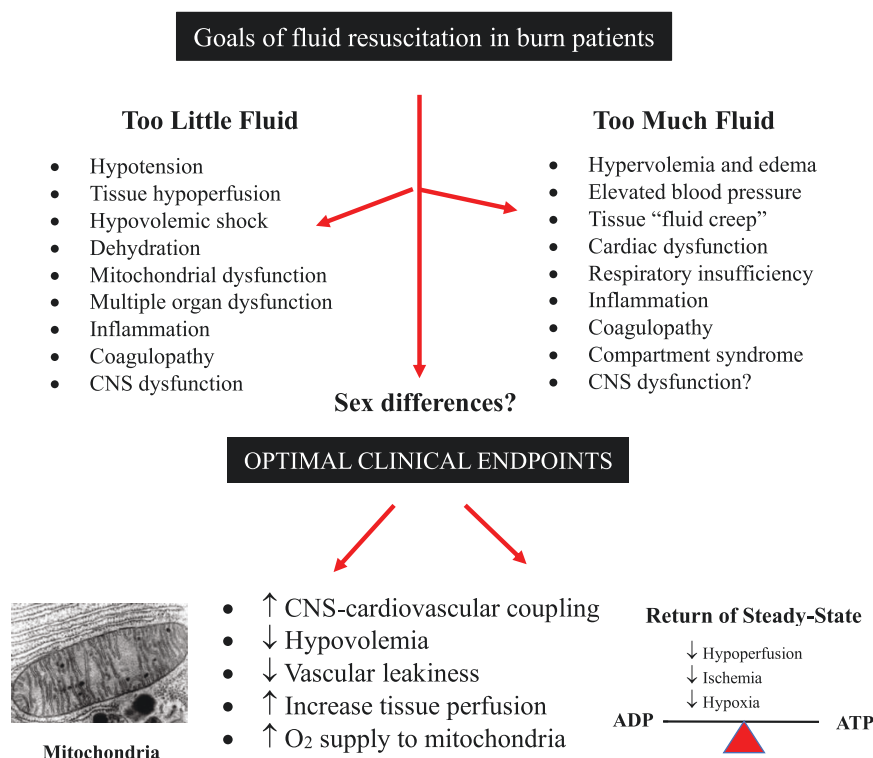
Myburgh (2018)<sup>89(p862)</sup>

Without adequate fluid resuscitation, severe burn patients are predisposed to develop hypovolemic shock, multiple-organ dysfunction, and possibly death.<sup>1,90</sup> Fluid therapy is therefore mandatory in adults (>15% TBSA) and critical in children (>10% TBSA).<sup>4</sup> Following a severe burn, plasma losses may exceed 4 mL per kilogram of body weight per hour.<sup>47,91</sup> *The primary goal of fluid therapy is therefore to prevent vascular leakage and hypovolemia and maintain adequate tissue perfusion and oxygenation* (Figure 3).<sup>80</sup>

Fluid therapy became a mainstay for burn patients in the early-to-mid 20th century.<sup>4,10,92,93</sup> A key proponent of fluid use was Yale's Frank Underhill who in the 1930s stressed the need to correct hypovolemia and blood thickening.<sup>92</sup> Underhill's recommendations were based on his clinical experience with burn patients following the Rialto Theater fire (New Haven, CT) in 1921 that killed 9 and injured ~80 people. Patients received an IV saline infusion of 25 mL/min supplemented by the drinking of water and other treatments.<sup>92</sup> Twenty years later, after another devastating fire at Cocoanut Grove nightclub (Boston, MA), 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.<sup>90,94</sup> Cope and Moore also formulated an IV fluid solution that comprised 50% plasma and 50% saline (Figure 1).<sup>94</sup> *These 2 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 (Figure 1).

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.<sup>90,91</sup> 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 × %TBSA × kg with the first half given in the first 8 hours, and the second half over the next 16 hours.<sup>91</sup> 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 (Figure 3).<sup>3</sup>



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.

**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 O<sub>2</sub> 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



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,<sup>95</sup> whereas colloid adjuncts appear less popular, as they remain highly controversial.<sup>4,10,93</sup> 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.<sup>89,91,96</sup> Possible trial complications include patient recruitment heterogeneity, differences in fluid responsiveness,<sup>97</sup> and difficulty in selecting the appropriate end points that *reflect improved tissue perfusion*. End points such as urine output >0.5 mL/kg per hour, base deficit <2, systolic blood pressure >90 mm Hg, and/or palpable pulse may not reflect adequate tissue perfusion (Figure 3).<sup>3</sup> 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)<sup>98(p842)</sup>

Burn injury is a devastating trauma. If polytrauma is present, morbidity and mortality are greatly increased, and females appear more vulnerable than males.<sup>14-17</sup> *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.*<sup>99</sup> Treating one symptom at a time can sometimes lead to what Shoemaker terms “contradictory therapeutic outcomes.”<sup>99</sup> 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.<sup>80</sup> 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.”<sup>100</sup> The key point is that despite generation of an overwhelming amount of mechanistic data 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 O<sub>2</sub> to mitochondria.<sup>44,80</sup> No such drug exists. The clinical end points to test such a drug would be a significant reduction in vascular leakage and rapid restoration of tissue O<sub>2</sub> *perfusion*. We have been developing an adenosine, lidocaine, and magnesium (ALM) fluid therapy for noncompressible hemorrhagic shock, traumatic brain injury,<sup>80,101</sup> and sepsis.<sup>102</sup>

The strategy being developed for far-forward battlefield and prehospital use is to administer a small volume of 3% NaCl ALM IV bolus followed 60 minutes later by a 0.9% NaCl ALM drip infusion for 4 hours.<sup>80,101</sup> We have shown in rat and pig hemorrhagic shock models that ALM therapy increases mean arterial pressure (MAP) from shock values (~30–40 mm Hg) into the permissive hypotensive range (MAP ~60 mm Hg), while providing neuroprotection and reducing secondary injury.<sup>80,103,104</sup> We have used this data to formulate a Systems Hypothesis of Trauma, which may also be applicable for severe burns.<sup>44,80</sup>

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<sub>2</sub> delivery in the first 8 hours.<sup>105</sup> 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 DAMP and PAMP 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.

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