

# Burns: Pathophysiology of Systemic Complications and Current Management

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As a result of many years of research, the intricate cellular mechanisms of burn injury are slowly becoming clear. Yet, knowledge of these cellular mechanisms and a multitude of resulting studies have often failed to translate into improved clinical treatment for burn injuries. Perhaps the most valuable information to date is the years of clinical experience and observations in the management and treatment of patients, which has contributed to a gradual improvement in reported outcomes of mortality. This review provides a discussion of the cellular mechanisms and pathways involved in burn injury, resultant systemic effects on organ systems, current management and treatment, and potential therapies that we may see implemented in the future. (J Burn Care Res 2017;38:e469–e481)

Burn injuries are a significant problem with more than 500,000 people seeking medical treatment, 40,000 resultant hospitalizations, and 4000 deaths per year in the United States.<sup>1</sup> The annual cost of treating these burns is estimated to be in excess of U.S. \$ 1 billion, not including the indirect costs of disability and rehabilitation.<sup>1</sup> These statistics have driven a multitude of studies that have systematically began to uncover the intricate mechanisms involved in burn and the complex pathophysiology of burn injury. Numerous mediators in these pathways have been the subject of animal studies in an attempt to find improved clinical therapies for treatment of burn injury. Unfortunately to date, few have translated into mainstream treatment options. Perhaps most frustrating is the lack of reproducibility of some animal studies and lack of effectiveness of potential therapies that have translated into clinical trials. On the other hand, years of clinical observations have led

to a decrease in mortality following burns.<sup>2</sup> This has led to a search for alternative approaches that can be used to indicate the performance of burn therapies.<sup>3</sup>

This review provides a discussion of the current understanding of cellular mechanisms and pathways involved in burn injury, resultant systemic effects on organ systems, current management and treatment, based on both animal and clinical studies, and potential therapies that we may see implemented in the future.

## CELLULAR MECHANISMS

The current understanding of burn wounds includes three zones of injury: zone of coagulation, zone of stasis, and zone of hyperemia.<sup>3</sup> The region of coagulation represents tissue that was destroyed at the time of injury. This is surrounded by a zone of stasis, with inflammation and low levels of perfusion.<sup>4</sup> Outside the zone of stasis is a zone of hyperemia, where microvascular perfusion is not impaired.<sup>4</sup> Often the area of stasis will progress and become necrotic within the first 48 hours following thermal injury.<sup>4</sup> As a result, the initial burn expands in area and depth. Thermal injury induces an immunosuppressed state that predisposes patients to sepsis and multiple organ failure.<sup>5</sup>

In assessing an approach to treat burn wounds, one must attempt to understand the numerous mechanisms behind the resulting microvascular dysfunction. Three main categories are commonly

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1559-047X/2016

DOI: 10.1097/BCR.0000000000000355

discussed in the literature. They include thrombosis of vessels due to vascular damage, upregulation of inflammatory mediators, and proapoptotic factors.

Nuclear factor  $\kappa$ B (NF- $\kappa$ B), a transcription activator protein, is activated immediately following severe burn injury (SBI) and is thought to regulate the induction of several inflammatory mediators, including tumor necrosis factor (TNF- $\alpha$ ).<sup>6</sup> Sequestered leukocytes in injured tissues are also thought to be a major source of proinflammatory mediators that cause microvascular damage.<sup>4</sup> The products released by tissue injury result in a biphasic response.

The first phase is the predominant proinflammatory phenomena known as systemic inflammatory response syndrome.<sup>7</sup> The central element is the macrophage cell and the biochemical cytokines TNF- $\alpha$  and interleukin-6 (IL-6).<sup>7</sup> Macrophages are major producers of proinflammatory mediators (ie, prostaglandin E2, reactive nitrogen intermediates, IL-6, TNF- $\alpha$ ).<sup>5</sup> Furthermore, thermal injury increases the production of these mediators by macrophages.<sup>5</sup> Thermal injury also results in prolonged and profound hypermetabolism that involves increased production of proinflammatory cytokines, as well as the formation of reactive oxygen species (ROS), such as superoxide anion, hydroxyl radical, hydrogen peroxide, and reactive nitrogen species, such as nitric oxide (NO) and peroxynitrite.<sup>8</sup> TNF- $\alpha$  is responsible in part for inducing apoptosis of various cell elements.<sup>7</sup> In addition, proapoptotic factors show increased expression including Bax, Bcl-xl, and caspase-3 activity. Furthermore, epidermal burn injury often triggers significant apoptosis of organ cells, which may be caused by a severe burn-induced systemic inflammatory reaction.

TNF- $\alpha$  also involves the antimicrobial defenses by activation of neutrophils and monocytes and also has the capacity to induce the secretion of other proinflammatory mediators, including IL-1 and IL-6.<sup>7</sup> However, of these proinflammatory cytokines, only IL-6 has consistently been shown to be elevated systemically post-burn.<sup>5</sup> In experimental animal models with third degree burns of either 20 or 40%, serum IL-6 levels peaked during the first hours after injury and were proportionate to the size of area burned.<sup>9</sup> During this early stage of burn injury, the inflammatory response can lead to organ failure, called early organ failure.

The second phase of a burn injury is predominantly anti-inflammatory.<sup>7</sup> This phase depends on T lymphocytes of helper Th-2 and three principal mediators: the cytokines IL-4/IL-10 and TGF.<sup>7</sup> This phase has become known as the counter anti-inflammatory response syndrome.<sup>7</sup>

These previously discussed inflammatory mediators along with the increase of vascular hydrostatic pressure caused by vessel dilation are the major reasons for systemic microvascular leakage observed in burns.<sup>10</sup> As a response to inflammation, the endothelial cell junctions widen and gaps form, resulting in compromised barrier functions.<sup>11</sup> One known mechanism behind these vascular changes involves actomyosin-dependent actin rearrangement.<sup>11</sup> Recently, it was discovered that thermal injury induces generalized venular hyperpermeability and that serum from burned rats induces endothelial cell actin rearrangement, contraction, as well as tight junction damage.<sup>12</sup> Studies show that exposure to burn serum results in a significant increase in endothelial permeability in a time-dependent manner, which is paralleled by a rapid and persistent activation of the p38 mitogen-activated protein kinase.<sup>13</sup> Inhibition of p38 mitogen-activated protein kinase largely ameliorates resulting vascular dysfunction.<sup>11,13</sup> The maintenance of normal vascular permeability depends on the integrity of endothelial barrier function regulated by the interaction of intracellular junctions, cell-matrix adhesion, and the cytoskeleton contractile force.<sup>10</sup> Furthermore, kinins, specifically bradykinin, are produced at the burn injury site.<sup>6</sup> Bradykinin is a powerful vasoactive mediator that causes venular dilation, increased microvascular permeability, smooth muscle contraction, and pain.<sup>6</sup>

After thermal injury, tissue adenosine triphosphate levels gradually fall, and increased adenosine monophosphate is converted to hypoxanthine, providing substrate for xanthine oxidase.<sup>14</sup> These complex reactions lead to deleterious free radicals, such as superoxide and hydrogen peroxide.<sup>14</sup> In addition to xanthine oxidase-related free radical generation in burn trauma, adherent-activated neutrophils produce additional free radicals.<sup>14</sup> Free radicals have been found to have beneficial effects on antimicrobial action and wound healing. However following a burn, there is an enormous production of ROS which is harmful and implicated in inflammation, systemic inflammatory response syndrome, immunosuppression, infection and sepsis, tissue damage, and multiple organ failure.<sup>15</sup> Thus clinical response to burn is dependent on the balance between production of free radicals and their detoxification.<sup>15</sup> Enhanced free radical production is paralleled by impaired antioxidant mechanisms, as indicated by burn-related decrease in superoxide dismutase, catalase, glutathione,  $\alpha$ -tocopherol, and ascorbic acid levels.<sup>15</sup> Burn-related upregulation of inducible NO synthase may produce peripheral vasodilation, upregulate the transcription factor NF- $\kappa$ B,

and promote transcription and translation of numerous inflammatory cytokines.<sup>14</sup> NO may also interact with the superoxide radical to yield peroxynitrite, a highly reactive mediator of tissue injury.<sup>14</sup> Free radical-mediated cell injury has been supported by post burn increases in systemic and tissue levels of lipid peroxidation products, such as conjugated dienes, thiobarbituric acid reaction products, or malondialdehyde (MDA) levels.<sup>14</sup>

Burn injury has recently been shown to result in a significant increase of hydrogen sulfide level ( $P < .01$ ) by 1.31-fold in the plasma.<sup>16</sup> This is due to the significant increase in hydrogen sulfide formed in liver after burn injury, which was enhanced by 1.23-fold compared with a control group ( $P < .01$ ).<sup>16</sup> This is significant due to new data supporting the proinflammatory role of hydrogen sulfide.<sup>16</sup> Injection of exogenous sodium hydrogen sulfide at the time of burn injury has been shown to significantly aggravate the systemic inflammatory response and increase multiple organ damage.<sup>16</sup>

Lipid mediators, including eicosanoids and recently discovered “specialized proresolution lipid mediators,” are key signaling molecules in the resolution of inflammation, playing a pivotal role in regulating the inflammatory profile and promoting return to homeostasis following burn.<sup>17</sup> Their dysregulation may lead to chronic inflammation and increased tissue damage.<sup>17</sup> Furthermore, these molecules have been shown to provide an ancillary treatment to antibiotics by increasing mucosal production of bactericidal peptides and enhancing bacterial phagocytosis by polymorphonuclear cells and macrophages.<sup>17</sup>

## EMERGING MECHANISMS INVOLVED IN BURN-INDUCED MICROVASCULAR INFLAMMATION

Mast cells (MC) are ubiquitous resident cells, conventionally regarded as effector cells of allergic reaction that can store and produce many mediators on activation.<sup>18</sup> MC are key contributors in blood coagulation and innate and acquired immunity.<sup>19</sup> Mounting evidence suggests that MCs, their tryptases, and their chymases play important roles in tissue repair.<sup>19</sup> While MCs initially promote healing, they can be detrimental if they are chronically stimulated or if too many become activated at the same time.<sup>19</sup> In fact, abnormal wound repair is associated with an increased number of MC strategically located around blood vessels.<sup>18</sup>

Thermal trauma has a direct effect on MCs, leading to the secretion of histamine.<sup>12</sup> Bankova et al.<sup>20</sup>

recently provided evidence that MC degranulation is virtually an instantaneous response following thermal injury. This leads to an increased xanthine oxidase activity and enhanced production of ROS, the latter being produced after burns through differing mechanisms.<sup>12</sup> ROS have been shown to have deleterious effects on cell membranes.<sup>12</sup> Thus, ROS could damage MC membranes leading to autoinjury due to the vasoactive actions of MC mediators. Santos et al.<sup>12</sup> suggested that ROS could potentially act as stimulators of MC degranulation in burns.

## SYSTEMIC EFFECTS

Severe burns induce response that affects almost every organ system.<sup>21</sup> Inflammation, hypermetabolism, muscle wasting, and insulin resistance are all hallmarks of the pathophysiological response to severe burns, with changes in metabolism known to remain for several years following injury.<sup>21,22</sup>

There are two phases of burn resuscitation. A resuscitation phase, also known as the “hypodynamic” or “ebb phase,” occurs first and lasts for approximately 24 to 72 hours.<sup>6,23</sup> This period is characterized by increased vascular permeability, fluid shifts resulting in intravascular volume depletion, and edema formation. The primary goal during this phase involves restoring and preserving tissue perfusion to avoid ischemia from hypovolemic and cellular shock.<sup>6,24</sup> Resuscitation is key during this phase. Multiple formulas are used but the most common is the Parkland formula, which is further discussed in the “Management” section. An imbalance between oncotic and hydrostatic forces can often develop.<sup>6</sup> Increases in microvascular permeability occur due to direct vascular thermal injury and through release of inflammatory mediators.<sup>6</sup> This increased vascular permeability leads to a shift of intravascular fluid and plasma proteins into the interstitial space resulting in decreased capillary oncotic pressure.<sup>6,23</sup> The new interstitial particles create an osmotic gradient that pulls additional fluid into the interstitium resulting in edema formation.<sup>6</sup> Hypoproteinemia occurs from loss of proteins into the edema fluid and from the injured skin surface.<sup>6</sup> Up to half of the total plasma water can be lost from the vascular compartment within 2 to 3 hours after a 40% TBSA burn.<sup>6</sup> Intravascular hypovolemia and a resulting hemoconcentration occur due to massive edema formation within the first 12 to 24 hours following injury.<sup>24</sup>

A “hyperdynamic and hypermetabolic flow phase” begins roughly 24 to 72 hours after injury.<sup>25</sup> This phase is characterized by a decrease in vascular permeability,

increased heart rate, and decreased peripheral vascular resistance resulting in an increase in cardiac output.<sup>6</sup> Approximately 24 to 48 hours after burn injury, the microvascular integrity begins to heal and peripheral blood flow is augmented by a decrease in systemic vascular resistance with preferential redistribution to the area of burn wounds.<sup>6,25</sup> Cardiac output is more than 1.5 times that of a nonburned, fit patient 3 to 4 days following burn injury.<sup>6,25</sup> Furthermore, metabolic rate is increased nearly three times that of their basal metabolic rate.<sup>6,25</sup>

## SKELETAL MUSCLE

Skeletal muscle is the primary site of peripheral glucose disposal and plays an important role in metabolic regulation.<sup>21</sup> Following a large burn, skeletal muscle functions as an endogenous amino acid store, providing fuel for more vital functions such as the synthesis of acute phase proteins and the deposition of new skin.<sup>21,26</sup> Another mechanism underlying critical illness-induced muscle wasting involves ubiquitin/proteasome-mediated protein degradation and/or apoptosis-mediated muscle mass loss.<sup>26</sup> For these reasons, burn patients tend to become cachectic.<sup>21,26,27</sup>

It can be argued that the loss in mitochondrial number and or function is just as important as the loss of muscle contractile proteins.<sup>21</sup> Severe burns are associated with rapid changes in skeletal muscle mitochondrial function.<sup>21,28</sup> Porter et al.<sup>27</sup> recently confirmed skeletal muscle mitochondria from burn victims are more uncoupled, indicating a source for greater heat production within skeletal muscle. These findings suggest that skeletal muscle mitochondrial dysfunction contributes to increased metabolic rate in burn victims.<sup>27</sup>

## CARDIOVASCULAR

One mechanism of burn-related cardiac dysfunction is believed to involve mitochondria. Mitochondria comprise roughly 35% of cardiomyocyte volume in the heart.<sup>29</sup> Zang et al.<sup>29</sup> used rats to show an accumulation of cytosolic cytochrome-c roughly three times that of control rats during the first 24 hours following burn-induced injury. Lipid peroxidation in cardiac mitochondria increased 30 to 50%, suggesting burn-induced oxidative stress.<sup>29</sup> Antioxidant therapy can be used to prevent burn-induced cardiac mitochondrial damage by decreasing lipid peroxidation and cytochrome-C release, enhance superoxide

dismutase, and glutathione peroxidase (GSH-Px) activity and improve resulting cardiac function.<sup>16,29</sup>

Another hallmark of SBI is tachycardia, increased myocardial oxygen consumption, and increased cardiac output.<sup>92</sup> Cardiac stress is largely mediated by an increased catecholamine response immediately following burn injury.<sup>30</sup>

Increasing evidence supports the role of inflammatory mediators contributing to cardiac damage following burn injury. Specifically, it has been hypothesized that following burn injury, cardiac dysfunction is related to macrophage migration inhibitor factor (MIF).<sup>6</sup> MIF has been found to play a role in adaptive and innate immunity, as an inflammatory cytokine, a neuroendocrine hormone, and catalytic enzyme.<sup>6,31</sup> MIF is released in response to burn injury by the skin and cardiomyocytes.<sup>32</sup> Willis et al.<sup>32</sup> evaluated mice that were subjected to 40% TBSA burn injury and MIF was found to be a critical mediator of late and prolonged cardiac dysfunction.<sup>6</sup> Mice treated with anti-MIF displayed rapid restoration of cardiac function with complete recovery by 24 hours.<sup>32</sup>

## RENAL

Defining acute renal failure in the burn population has been problematic, with various studies reporting ranges from 0.5 to 30%.<sup>22,33</sup> In the past, the International Acute Dialysis Quality Initiative group standardized the definition of acute renal insufficiency by developing the RIFLE criteria.<sup>22,33</sup> The RIFLE criteria define three different grades of acute renal injury (risk, injury, and failure) based on glomerular filtration rate, urine output, and two clinical outcome parameters (loss and end-stage kidney disease).<sup>22,33</sup> In 2007, the Acute Kidney Injury Network (AKIN) developed a modified standard for diagnosis and classifying acute kidney injury (AKI). Chung et al.<sup>34</sup> compared a cohort of patients using the RIFLE criteria and AKIN criteria. The determined in-hospital mortality was significantly higher using the AKIN criteria at 0.877 (95% confidence interval: 0.848–0.906) when compared with the RIFLE criteria at 0.838 (95% confidence interval: 0.801–0.874;  $P = .0007$ ).<sup>34</sup> The results of this study suggested that the AKIN criteria may be more precise and more predictive of death than the RIFLE criteria.<sup>34</sup>

AKI related to thermal injury is most likely to occur at two distinct time points: early during resuscitation or late secondary to sepsis.<sup>22</sup> Early AKI has been shown to be associated with early multiple organ dysfunction and higher mortality risk.<sup>35</sup> Increasing size and depth of burns are key factors

determining AKI.<sup>33</sup> Prevention of AKI requires early and aggressive fluid resuscitation and preservation of normal renal perfusion.<sup>22</sup> Global parameters of perfusion (lactate, base deficit, and central venous saturation) are **more appropriate than urine output** alone in reflecting the degree and recovery from a hypoperfused state, or a state of shock.<sup>22</sup>

The pathophysiology of late AKI is altered from that of early AKI, and remains a serious problem within the burn intensive care unit.<sup>22</sup> **Sepsis or septic shock** accounts for up to **87% of the** cases of acute renal failure within the burn intensive care unit.<sup>22</sup> Late AKI is multifactorial, but primarily relates to the systemic inflammatory response that accompanies a septic event such as generalized vasodilation and a hypercoagulable state.<sup>22</sup> These result in AKI via a **decrease in renal perfusion**: globally via vasodilation resulting in decreased systemic blood pressure and **locally** by formation of **microthrombi** in the glomeruli.<sup>22</sup> Ultimately, **renal replacement therapy** has been shown to be **only marginally effective in reducing mortality** rates, and prevention still serves as the most effective treatment.<sup>22,33</sup>

## PULMONARY

Patients with systemic burn injuries often have associated **smoke inhalation injury**.<sup>36</sup> Swanson et al.'s<sup>36</sup> retrospective study of the National burn repository database (n = 5975) during a 12-year period showed that **lung injury** was the **second most common cause of death in the first week (16%)** following burn injury, second only to **burn shock (62%)**. Inhalation injury disrupts the supply of oxygen to the body by **immense swelling of the upper respiratory tract, chemical irritation of the lower respiratory tract, and injuries resulting from noxious gases**, such as **carbon monoxide and cyanide**.<sup>37</sup> Several common clinical consequences in patients with smoke inhalation injury include acute upper airway obstruction, bronchospasm, small airway occlusion, pulmonary infection, and respiratory failure.<sup>37</sup>

Thermal injury and adherence of irritants to the upper respiratory tract results in the release of **inflammatory mediators and ROS**, increased vascular **permeability**, and **edema formation**. The edema in the upper respiratory tract can progress to airway **obstruction and bronchospasm that peaks at 24 hours**.<sup>6</sup> Hemorrhage, mucosal congestion, ulceration, and **laryngospasm** may also occur **within the first 24 hours**.<sup>6</sup> The damaged mucosal cells produce excess exudates rich in protein, inflammatory cells, and **necrotic debris**.<sup>6</sup> The release of these

inflammatory mediators such as IL-1a, IL-6, IL-8, and TNF- $\alpha$  are **chemotactic to neutrophils**.<sup>25</sup> Neutrophils migrate through the glandular epithelium and into the airway lumen.<sup>25</sup> The resultant damage to the columnar epithelia inhibits the mucociliary apparatus of the trachea **allowing distal migration of upper airway material and bacteria**, leading to distal obstruction and potential **infection**.<sup>6</sup>

With severe burns, respiratory failure can occur and is generally characterized by hypoxemia with evolution to acute lung injury or acute respiratory distress syndrome (**ARDS**).<sup>4,38</sup> ARDS is a leading cause of mortality in burn patients.<sup>39</sup> The Berlin definition of ARDS is currently the most accurate criteria for determining ARDS.<sup>39</sup> This includes three categories of ARDS based on degree of hypoxemia: **mild ( $200 \text{ mm Hg} \leq \text{PaO}_2/\text{FiO}_2 \leq 300$ )**, **moderate ( $100 \text{ mm Hg} \leq \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$ )** and **severe ( $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$ )**, with a **PEEP  $\geq 5 \text{ cm H}_2\text{O}$** .<sup>39</sup> As far as treatment, Asmussen et al.<sup>39</sup> conducted a meta-analysis and determined that there is currently **no improvement in survival for burn patients suffering acute hypoxemic respiratory failure with the use of extracorporeal membrane oxygenation**.

Management of inhalation injury consists of supportive care as no clear standard treatment has been shown to improve clinical outcomes.<sup>4</sup> Cincinnati Shriners Hospital for children recently retrospectively examined an **anti-inflammatory pulmonary enteral nutrition formula** previously used in adults. Patients had a  $\text{PaO}_2/\text{FiO}_2$  ratio  $<200 \text{ mm Hg}$  with median burn size of 36% TBSA at the time of specialized nutrition support. Ultimately, 17 of 19 patients survived.<sup>38</sup> Improvements were seen in respiratory function, chemistries, including blood urea nitrogen, creatinine, sodium, and potassium.<sup>38</sup> In another study by Elsharnouby et al.,<sup>40</sup> it was found that **nebulized heparin 10,000 international unit (IU)** decreased lung injury scores and duration of mechanical ventilation but had **no effect on length of ICU stay and mortality**. These limited studies support further evaluation of specialized treatments to reduce lung injuries and improve clinical outcomes.

In a survey of mechanical ventilator practices across burn centers in North America by Chung et al.,<sup>41</sup> pressure support and volume assist control were the most common mechanical ventilation modes used in burn patients with or without inhalation injury. In the setting of Berlin defined mild ARDS, ARDSNet protocol and optimal positive end-expiratory pressure were the most common treatments used with fluid restriction/diuresis employed as a nonventilator adjunct.<sup>41</sup> For severe ARDS, airway pressure release ventilation and neuromuscular blockade were most often used.<sup>41</sup>

## NEUROLOGICAL

Cellular hypoxia leads to an increase in intracranial pressure and cerebral edema formation.<sup>42,43</sup> Other signs of CNS dysfunction can include agitation, confusion, ataxia, abnormal posturing, transient loss of consciousness, seizures, and even shock.<sup>43</sup>

After a deep burn injury, cutaneous nerve regeneration will occur with the migration of new nerve fibers from the wound bed or from the collateral sprouting of nerve fibers from adjacent uninjured area.<sup>44</sup> This nerve regeneration process is imperfect. It was reported that 71% of extensively burned victims suffer from abnormal sensation and 36% from chronic pain.<sup>44</sup> Critical illness polyneuropathy in burn patients is an underreported condition in burn patients.<sup>45</sup> It is associated with high mortality rates and prolonged hospital stay and rehabilitation.<sup>46,47</sup> There is a strong link to sepsis, multiple organ failure, and slow ventilator wean.<sup>46,47</sup>

Recent studies on rats have shown that vagus nerve stimulation improved thermal injury-induced shock symptoms.<sup>43,48</sup> The severity of metabolic acidosis was limited in severity and the elevation of pro-inflammatory cytokines such as TNF- $\alpha$  and IL-6 was attenuated significantly.<sup>43,48</sup> This may serve as a useful mechanism in battling systemic effects of thermal injury in the future.

## GASTROINTESTINAL

After a thermal injury, blood flow to the bowel decreases by nearly 60% of baseline and stays decreased for up to 4 hours.<sup>49</sup> Intraabdominal hypertension (IAH) and secondary abdominal compartment syndrome (ACS) are potential sequelae to systemic burn injuries, occurring in as many as 36 to 70% and 1 to 20% of burn patients, especially in patients with burns of >60% BSA.<sup>42,50-52</sup> It is currently unknown if these syndromes are iatrogenic consequences of excessive or poorly managed fluid resuscitation or unavoidable sequelae of the primary injury.<sup>50</sup>

Intraabdominal pressure (IAP) can be altered by decreased abdominal wall compliance resulting from circumferential torso burns and tension secondary to pain or discomfort.<sup>42,52</sup> As IAP increases, IAH will eventually result.<sup>42</sup> If IAH goes unnoticed or left untreated, ACS develops resulting in pressure-induced organ dysfunction and failure.<sup>42,52</sup> ACS is commonly associated with prolonged IAP pressures of >20 mm Hg.<sup>50</sup> Percutaneous drainage and escharotomy may reduce IAP in the case of abdominal burns.<sup>51</sup> The standard treatment is laparotomy, with mortality rates reported to be as high as 75% in patients with ACS.<sup>53</sup>

## HEPATIC

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels are increased immediately after burn injuries and are the most sensitive indicators of hepatocyte injury.<sup>54</sup> ALT is the more sensitive and specific test for hepatocyte injury as AST also can be elevated in a state of cardiac arrest or muscle injury.<sup>54</sup> These levels have been shown to remain elevated for a period of 4 to 6 weeks.<sup>49,54</sup>

Liver damage has been shown to be associated with an increased hepatic edema formation.<sup>49,54</sup> Liver weight significantly increases 2 to 7 days after burn.<sup>47</sup> Because hepatic protein concentration is significantly decreased in burn models for up to 9 months after burn injury, it has been suggested that the liver weight gain is caused by the increase in edema formation rather than by the increases in the number of hepatocytes or protein synthesis.<sup>49,54</sup> Liver size and weight significantly increase during the first week and peak 2 weeks after injury.<sup>54</sup> At 12 months, the weight can still be increased by 40 to 50% compared with the predicted liver weights.<sup>54</sup>

## MANAGEMENT

The burn injured patient is distinctive in resuscitation requirements, metabolic stress, pattern of complications, and determinants of outcome when compared with other forms of trauma.<sup>38</sup> Fluid resuscitation in burn patients is critical. The Parkland formula proposed by Baxter and coworkers in the 1960's is still widely used today ( $IVF = TBSA \text{ burned } (\%) \times \text{weight } (kg) \times 4 \text{ ml}$ ).<sup>38,55</sup>

Excessive fluid resuscitation increases the chances for extremity compartment syndromes, ACSs, and ARDS.<sup>55</sup> It has been suggested that excessive narcotic use or "opiod creep" can further contribute to this initial excessive fluid resuscitation.<sup>55</sup> To avoid these undesired consequences of over resuscitation, however common or uncommon, the basics of any initial resuscitation formula are to provide a balanced salt solution with total volume infused during the first 24 hours proportional to the affected BSA and the patient's body weight.<sup>22</sup> The rate of volume infused is calculated by delivering half of the volume during the first 8 hours and the remainder during the following 16 hours.<sup>22</sup>

The primary goal of nutritional support in burn patients is to satisfy acute, burn-specific requirements, and not to overfeed.<sup>56</sup> Attempting to overcompensate and provide excess calories and/or protein is ineffective and likely to lead to increased complications, such as hyperglycemia, carbon dioxide retention

(CO<sub>2</sub>), and azotemia.<sup>56</sup> Patients treated with oral alimentation alone can lose up to 25% of their pre-admission weight by 3 weeks after injury and is thus inadequate.<sup>56</sup> Total parenteral or enteral nutrition allows for elemental components that do not require digestion or a functioning alimentary tract.<sup>56</sup> Today, most clinicians prefer to use enteral nutrition with a high carbohydrate diet consisting of 82% carbohydrate, 3% fat, and 15% protein.<sup>22</sup> This diet has been suggested to stimulate protein synthesis, to increase endogenous insulin production, and to improve overall lean body mass in comparison with alternative formulas.<sup>22</sup> Dextrose is the main calorie source used and the recommended carbohydrate intake in adults is between a baseline of 2 g/kg/d and the maximum rate at which glucose can be assimilated in severely burned patients (7 g/kg/d).<sup>56,57</sup> There is evidence increasing protein requirements from 1 g/kg body weight per day to 1.5 to 2 g/kg body weight per day may be beneficial.<sup>30,57</sup> Any higher amount of supplementation may lead to increased urea production without improvements in lean body mass or muscle protein synthesis.<sup>30</sup> Lipid emulsions can also comprise a significant proportion of the calories in TPN, although diets with majority carbohydrate content are preferred.<sup>30</sup> Adults can maintain body weight after SBI only with aggressive and continuous nutrition of 25 kilocalories per kilogram body weight per day plus 40 kilocalories per percent TBSA burn per day.<sup>30,56,57</sup> Optimal nutritional support for the severely burned patient is accomplished best by early initiation of enteral nutrition as this can modulate the hypermetabolic response of severe burns.<sup>30,56,57</sup> Oxandrolone, a testosterone analog, has been demonstrated to improve net nitrogen balance, decrease weight loss, and shorten overall length of hospital stay.<sup>22,28</sup> These improvements in muscle metabolism and protein synthesis have been observed in both the pediatric and adult burn populations.<sup>22,28</sup> It should be noted that this hyperdynamic circulation and increased metabolic rate can continue up to 2 years following burn injury in people.<sup>6</sup>

Treating burns requires the toxic eschar be removed early, usually in the first 24 to 72 hours.<sup>30,58</sup> Removal of necrotic tissue reduces mortality and complications in patients with serious burns.<sup>30</sup> This is typically achieved through surgical eschar excision and split thickness auto grafts from healthy skin.<sup>30,58</sup> Thus, burn treatment strategies often are limited by available amounts of healthy skin still present.<sup>43,58</sup>

Topical antimicrobial agents should be administered after initial decontamination to prevent bacterial colonization of the burn wound.<sup>42</sup> Systemic agents are less successful in treating local infections

because they do not reach the burn wounds in large concentrations due to the microthrombosis of vessels and wound edema.<sup>42</sup> The area is then covered with a nonadherent dressing.<sup>42</sup>

## CURRENT AND EMERGING THERAPEUTIC TREATMENTS

Following burn injury, due to the resultant oxidative stress, there is an increased requirement for vitamin C as indicated by the reduced vitamin C blood levels seen in burn patients.<sup>59</sup> Repeated studies have reported decreased serum levels of vitamin A and C following thermal injury.<sup>60</sup> Vitamin A serum levels have been shown to be reduced after thermal injury and persist for over 30 days, a phenomenon associated with the decrease in plasma transthyretin and retinol binding protein levels.<sup>60</sup> The low levels of vitamin C observed can be explained by cutaneous loss of ascorbic acid and larger expenditure in extracellular compartments, neutralizing free radicals and aiding regeneration of vitamin E.<sup>60</sup> This may explain why vitamin E levels often remain stable following thermal injury.<sup>60</sup> Regardless, there is substantial experimental and clinical evidence to show a codependence of vitamins E and C in antioxidant defense.<sup>61</sup>

Numerous studies have revealed that vitamin C (as ascorbate) can be valuable in the treatment of burn patients.<sup>59,62,63</sup> However, of critical importance with regards to vitamin C, is the fact that there is good evidence to indicate parenteral high dose administration is required to attain therapeutic concentrations.<sup>59,62,63</sup> This likely explains the failure of many studies of oral vitamin C to show any clinical benefit in cardiovascular disease and various other forms of endothelial damage.<sup>59</sup> Parenteral high-dose vitamin C inhibits endotoxin-induced endothelial dysfunction and vasohyporeactivity and works to reverse sepsis-induced suppression of microcirculatory control in rodents.<sup>59,62,63</sup> Parenteral high-dose vitamin C also has been shown to significantly reduce required resuscitation fluid volumes in both humans and animals.<sup>62</sup> The use of parenteral high dose vitamin C has been recommended to reduce acute smoke inhalation injury.<sup>64</sup>

In a controlled clinical study, burn patients were treated with a dose of vitamin C 66 mg/kg/hr for 24 hours. This corresponds to 110 g of vitamin C in a patient weighing 70 kg.<sup>59</sup> The 24-hour fluid resuscitation volumes in burn patients in the control and ascorbic acid groups were 5.5 ± 3.1 vs. 3.0 ± 1.7 (*P* < .01).<sup>59</sup> The length of required mechanical ventilation in the control and ascorbic acid groups was 21.3 ± 15.6 and 12.1 ± 8.8 days, respectively

( $P < .05$ ).<sup>59</sup> Administration of high-dose vitamin C during the first 24 hours after thermal injury also significantly reduced weight gain, wound edema, and a decrease in the severity of respiratory dysfunction.<sup>59,62</sup>

One key fact with regard to medical management of patients being treated with high doses of vitamin C is the inaccurately high point of care glucose (POCG) readings observed.<sup>65</sup> Kahn and Lentz<sup>65</sup> showed that mean POCG ( $225 \pm 71$ ) was significantly higher than laboratory glucose ( $138 \pm 41$ ;  $P = .002$ ).<sup>65</sup> Inaccurate POCG could potentially lead to iatrogenic hypoglycemia and even seizures if the fictitious hyperglycemia is treated with insulin.

Recent studies suggest melatonin attenuates damage to endothelial adherens junctions and helps prevent resulting microvascular hyperpermeability.<sup>66</sup> Melatonin has been shown to be a scavenger of hydroxyl, peroxy, and superoxide radicals.<sup>29</sup> Furthermore, melatonin has the ability to stimulate the activity of antioxidant enzymes, such as glutathione reductase, GSH-Px, catalase, and superoxide dismutase.<sup>61</sup> In vivo, melatonin stimulates the immune system, increasing T cell activity, lymphocyte growth, and humoral responses and possibly inhibiting thymus involution with age.<sup>61</sup> Furthermore, treatment with melatonin decreases elevated hepatic NF- $\kappa$ B activity and TNF- $\alpha$ , and suppressed the elevation of plasma AST and ALT levels.<sup>67</sup> These combined actions of melatonin, along with its low toxicity and its ability to penetrate morphophysiological membranes, could make it a highly beneficial treatment in burn patients.<sup>68</sup>

N-acetylcysteine (NAC) is an antioxidant administered in both oral and injectable forms.<sup>69</sup> Recent data have shown that NAC treatment increased the level of endogenous antioxidants and diminished interleukin production in the acute phase of burn trauma.<sup>70</sup> One potential mechanism was proposed is that NAC is an effective inhibitor of TNF- $\alpha$ , IL-1 $\beta$ , and IL-8 release in endothelial and epithelial cells.<sup>70</sup> Animal models have shown that the administration of NAC increased glutathione and decreased MDA levels in the lung 1 hour and 1 day after burn.<sup>71</sup> Tsai et al.<sup>69</sup> showed that treating burns with NAC 3.0% resulted in better re-epithelialization.

Insulin treatment has been effective at treating post burn hyperglycemia. Elevated plasma glucose levels have been shown to suppress immune function by altering macrophage cytokine production.<sup>28</sup> Immune function is further affected by elevated glucose levels, which lead to immunoglobulin glycosylation when glucose levels are  $>220$  mg/dl, reducing opsonic activity.<sup>28</sup> In the critically ill, survival and morbidity improve when blood glucose levels are

maintained at  $<110$  mg/dl.<sup>28</sup> Glucose control is also associated with improved wound healing.<sup>28</sup> In addition to providing the benefits of normoglycemia and wound healing, continuous infusions of this anabolic peptide in severe burn patients prevent breakdown of muscle protein and maintain lean mass.<sup>28</sup> Metformin appears to have effects analogous to insulin in critically injured patients and is a promising alternative given its side effect profile in the outpatient setting.<sup>28</sup>

In burn patients, insulin resistance persists for at least 9 months and up to 3 years after hospital discharge.<sup>72</sup> Several studies have demonstrated that pharmacological interventions such as peroxisome proliferator-activated receptors- $\alpha$  agonists and intensive insulin therapy are a viable means of augmenting skeletal muscle mitochondrial function post burn.<sup>21,72</sup> Propranolol and or oxandrolone treatment have also both been shown to mitigate skeletal muscle catabolism post burn and additional studies are needed to determine the effects of these drugs on mitochondria function within skeletal muscle remains.<sup>21,73</sup>

Ghrelin has been shown to be a natural ligand of the orphan growth hormone secretagogue (GHS) receptor type 1a (GHS-R1a).<sup>8</sup> GHS receptors are present in several areas of the CNS and in peripheral tissues, which indicates that ghrelin has various effects in addition to the release of GH. In a recent study, ghrelin was found to have a neutrophil dependent anti-inflammatory effect that prevents burn-induced damage in skin and remote organs and protects against oxidative organ damage.<sup>8,74</sup> The peptide acts via GHS-R to specifically inhibit the expression of proinflammatory cytokines, such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$ .<sup>8,74</sup>

Ulinastatin is a urinary trypsin inhibitor that has been shown to have beneficial effects in minimizing the damage of AKI after burn.<sup>75,76</sup> Although ulinastatin has no statistically significant effects on the blood urea nitrogen and serum creatinine levels, it can significantly reduce renal interstitial injury and suppress interstitial collagen deposits.<sup>76</sup> The renoprotective effect of ulinastatin is likely due to its down regulation on the TGF- $\beta$ /Smad signaling pathways.<sup>76</sup>

The burn-induced stress response results in the secretion of endogenous catecholamines, which are thought to be the primary mediators of hypermetabolism after severe burns.<sup>28,56</sup> There is a 10- to 50-fold elevation of plasma catecholamines and corticosteroid levels that last up to 12 months post burn.<sup>56</sup> Drugs that block this catecholamine surge have been shown to be effective at countering

catecholamine-induced sequelae after severe burns.<sup>28</sup> Catecholamines increase myocardial oxygen consumption. Administering low doses of propranolol (0.5–1.0 mg/kg) to severely burned patients reduces myocardial oxygen requirements without adversely affecting oxygen delivery.<sup>28,56</sup> Randomized controlled trials suggest that propranolol works in a dose-dependent manner to reduce cardiac work load in severely burned children.<sup>28,77</sup> Analysis of a large randomized-control trial to assess the efficacy and safety of long-term propranolol in severely burned pediatric patients revealed that a decrease in heart rate of 15% below admission heart rate and the accompanied decrease in cardiac work are maintained with an average dose of 4 mg/kg/d.<sup>28,77</sup> Furthermore, both local and systemic administration of propranolol has been shown to enhance wound healing and decrease the surface area requiring skin grafting.<sup>28</sup>

## LIPOIC ACID

Alpha-lipoic is a catalytic agent for oxidative decarboxylation of pyruvate and  $\alpha$ -ketoglutarate, and it has been extensively studied for its role in energetic metabolism and protection from ROS-induced mitochondrial dysfunction.<sup>78</sup> Many studies have reported  $\alpha$ -lipoic acid can regulate the transcription of genes associated with antioxidant and anti-inflammatory pathways.<sup>45,78–80</sup> Uyar et al. showed that treatment with lipoic acid after invasive surgeries attenuated the acute inflammatory response by decreasing levels of IL-6, IL-8, C3, and C4 levels.<sup>45</sup> Alpha-lipoic acid has also been reported to increase aldehyde dehydrogenase-2 activity in cultured cells.<sup>81</sup> Aldehyde dehydrogenase-2 is the main enzyme responsible for acetaldehyde oxidation in ethanol metabolism and also provides protection against oxidative stress.<sup>79</sup>

Several individual studies have focused on the effects of  $\alpha$ -lipoic acid mediating damage post artificially induced damage. Alpha-lipoic acid was found to lessen oxidative stress and to lead to increased levels of catalase, GSH-Px, and glutathione, while decreasing MDA levels in artificially induced lung injuries in rats.<sup>80</sup> This shows that lipoic acid appears to have protective effects against acute lung injury and has great potential for prevention of acute lung injury in thermal burns.<sup>80</sup> In spleen homogenates, the early administration of  $\alpha$ -lipoic acid after LPS challenge suppressed symptoms of oxidative stress and inflammation, seen as an increase in  $-SH$  groups and a decrease in TNF- $\alpha$  levels.<sup>82</sup> In another related study, providing birds with 300 mg/kg  $\alpha$ -lipoic acid

before exposure to aflatoxin B1 prevented increase in malondialdehyde levels and maintained steady GSH-Px and glutathione levels in the liver.<sup>81</sup> Lipoic acid treatment also has been shown to markedly reduce increases in serum ALT and AST levels, suggesting a protective effect on hepatic damage.<sup>83</sup>

## Clinical Trials

As a result of many years of research, the understanding of the pathophysiology of burn injury has continued to expand. Yet better knowledge of these cellular mechanisms has resulted in relatively modest improvements in clinical treatments. Several factors may contribute to the discrepancy between the effectiveness of therapies in basic science studies and results of clinical trials. First, there is always the possibility of species differences in the mechanisms underlying responses to burns. In addition, various models have been used in animals to induce cutaneous burns, such as exposure to steam, direct thermal injury as well as other approaches. Each model has inherent limitations in replicating the clinical situation. In addition, some basic science studies have demonstrated beneficial effects of various agents given before induction of burns, which has limited clinical relevance.

Furthermore, there are successful treatments in animal studies that have yet to be tested in clinical trials. An example of clinical trials lagging behind animal studies is ancillary treatments used in conjunction with ventilatory support, many of which were discussed previously. A small, retrospective, single-center study with 30 patients using historical controls and receiving the same ventilatory strategy found a 38% decrease in mortality and reduced lung injury scores when nebulized unfractionated heparin, N-acetylcysteine and albuterol sulfate were administered in comparison with albuterol.<sup>84</sup> A pediatric case series with historical controls similarly found a significant decrease in mortality, incidence of atelectasis and reintubation rate in a group treated with an alternating regime of aerosolized heparin alternating with 20% N-acetylcysteine solution.<sup>84</sup> Yet, a multicenter, prospective trial is still needed to confirm these data as reliable and reproducible before it can be accepted as a new standard of care.<sup>84</sup>

Another challenge with clinical trials is observed when different studies report conflicting results. An example of conflicting data seen in clinical trials is the debate on which form of fluid resuscitation is most effective. Some have argued that administration of hypertonic hydroxyethyl starch 200/0.5 (10%) administered in combination with crystalloids

within the first 24 hours after injury can improve survival rates.<sup>85</sup> However, Béchir et al.<sup>85</sup> showed that rather than a benefit in treatment, there was an increased mortality and should therefore be used with caution moving forward. This is also seen with NO, which has been used in burn patients to treat hypoxic pulmonary vasoconstriction and to improve ventilation/perfusion mismatches and therefore tissue oxygenation. This is also seen with nitric oxide, which has been used in burn patients to treat hypoxic pulmonary vasoconstriction and to improve ventilation/perfusion mismatches and therefore tissue oxygenation.<sup>84</sup>

A recent meta-analysis of burn patients with oxandrolone showed significant benefits, such as decreased body mass loss, nitrogen loss, and donor area healing time.<sup>86</sup> Yet, many centers still refrain from the use of oxandrolone due to previously reported risks not observed in this study.<sup>86</sup> As is the case with many topics related to management of burns, the meta-analysis strongly encouraged a randomized, double blind study, with a larger number of patients to obtain quality evidence for the testosterone analog.<sup>86</sup> Yet, with some institutions already empirically treating patients with oxandrolone before initiation of a clinical trial, a prospective trial to evaluate the effectiveness of the drug has yet to occur.

Clinical observation also leads to clinical trials. However, due to the complex mechanisms involved with burn, simple supplementation of an observed deficiency has often resulted in frustrating outcomes. For example, children suffering severe burns are known to develop progressive vitamin D deficiency because of inability of burned skin to produce normal quantities of vitamin D<sub>3</sub> and lack of vitamin D supplementation on discharge.<sup>87</sup> Yet, supplementation of burned children with a standard multivitamin tablet stated to contain 400 IU of vitamin D<sub>2</sub> failed to correct the vitamin D insufficiency.<sup>87</sup>

## POSSIBLE APPROACHES FOR THE FUTURE

Burns not only destroy the barrier function of the skin but also alter the perceptions of pain, temperature, and touch. It has been demonstrated in the past that hematopoietic stem/progenitor cells, as well as pluripotent very small embryonic-like stem cells, are mobilized into peripheral blood in patients and experimental animals in response to tissue/organ injury.<sup>88</sup> This phenomenon indicates an intrinsic mechanism involving circulating stem cells must exist to ameliorate tissue damage.<sup>88</sup>

With the ever advancing field of stem cell research and the seriousness of burn injuries, recent studies have attempted to use stem cells to improve burn injury outcomes.<sup>88-90</sup> Several approaches have been proposed, including coverage of damaged skin by artificial skin equivalents, topical application of expanded keratinocytes, or engraftment of bone marrow-derived cells.<sup>88</sup>

Cell therapy is therapeutic administration of living cells aimed at tissue regeneration, support for any defective function (such as wound healing), and modulation of pathophysiological processes (such as hyperinflammation or immune dysfunction).<sup>58</sup> Epithelial sheets can be directly grafted on donor sites to accelerate and improve their regeneration to harvest split-thickness autografts faster and several times from the same donor site. Alternatively, epithelial sheets can also be grafted alone on debrided burns, with less optimal healing quality, or in combination with a widely meshed split-thickness autografts for a better aesthetic result.<sup>58</sup> Ultimately, the reconstruction of a complete tissue-engineered skin featuring both the epidermis and the dermis is the goal to improve healing quality and avoid scar formation.<sup>44,58</sup> Cultured epidermal autografts have a couple major drawbacks: fragility, high cost, and poor cosmetic quality of healed zones, mostly due to their lack of underlying dermis, which results in an immature dermal-epidermal junction.<sup>48</sup> Mesenchymal stem cells (MSCs) could provide an answer to all of these drawbacks.

The ability of MSCs to differentiate into multiple different cell lineages and produce important growth factors and cytokines has stimulated research into their use burn injuries.<sup>75,88-90</sup> Liu et al. showed that when MSCs were grafted onto burn wounds, the skin showed better healing and keratinization, less wound contraction, and more vascularization.<sup>90</sup> Although MSCs with self-renewable and multipotential properties provide a vital modality of repair and regeneration, their vitality varies according to the donor age and health condition.<sup>75,85,86</sup> Research in recent years has suggested that umbilical cord-derived MSCs exhibit higher occurrence of colony-forming unit fibroblast than bone marrow-derived MSCs, suggesting more primitive features.<sup>75</sup>

The potential advantages of using MSCs cannot be discussed without also mentioning future challenges. MSCs have been shown, by at least two mechanisms, to promote malignancy in animal models.<sup>58</sup> They are suspected of providing a microenvironment capable of sustaining tumor growth, and their own malignant transformation has also reported by culturing them, ex vivo.<sup>58</sup> More research into the potential

advantages, as well as finding ways to eliminate potential disadvantages, is necessary before this treatment can be introduced.

## CONCLUSION

In recent years, advances have been made in the overall understanding of burn injury. Basic science studies have slowly begun to uncover the complex mechanisms involved in the systemic response to burn. Clinical trials are still largely limited to the assessment of managing and treating burn injuries. Thus, treatment advancements have come in part through observation of physicians in the clinical setting. Translation of results from basic science studies to improved clinical therapies for treatment of burn victims has been modest, and increased numbers of clinical trials of novel therapeutic approaches for burn should be a priority in the years ahead.

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