

Review

Bench-to-bedside review: Burn-induced cerebral inflammation – a neglected entity?

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Abstract

Severe burn injury remains a major burden on patients and healthcare systems. Following severe burns, the injured tissues mount a local inflammatory response aiming to restore homeostasis. With excessive burn load, the immune response becomes disproportionate and patients may develop an overshooting systemic inflammatory response, compromising multiple physiological barriers in the lung, kidney, liver, and brain. If the blood–brain barrier is breached, systemic inflammatory molecules and phagocytes readily enter the brain and activate sessile cells of the central nervous system. Copious amounts of reactive oxygen species, reactive nitrogen species, proteases, cytokines/chemokines, and complement proteins are being released by these inflammatory cells, resulting in additional neuronal damage and life-threatening cerebral edema. Despite the correlation between cerebral complications in severe burn victims with mortality, burn-induced neuroinflammation continues to fly under the radar as an underestimated entity in the critically ill burn patient. In this paper, we illustrate the molecular events leading to blood–brain barrier breakdown, with a focus on the subsequent neuroinflammatory changes leading to cerebral edema in patients with severe burns.

Introduction

Severe burn injury remains a significant health issue for society and a life-threatening event for the victim. Each year, more than 1.2 million people in the United States alone suffer burn injuries [1]; some 100,000 of these patients are hospitalized, accounting for a total of 2 million hospital days [2]. Thermal injuries mainly affect patients younger than 50 years of age [3] and remain one of the leading causes of childhood deaths, according to the Children's Burn Awareness Program. While the overall mortality has been reported to be 5%, it rapidly increases with advancing age and burn size up to 96% [3]. Most fatalities (65%) seem to be linked to burn-induced multiple organ failure, and 93% of burn patients

present with clinical signs of the systemic inflammatory response syndrome before succumbing to their injuries [4].

One of the critically impaired yet frequently overlooked organs in severe burn victims is the brain, despite the fact that cerebral complications in severe burn victims have been shown to highly correlate with mortality [5]. Hypoxic brain injury has been found as a primary cause of death in up to 10% of severe burn patients in an age-dependent manner [6]. The present review focuses on the neuroinflammatory changes occurring after severe burn injury and on the molecular mechanisms involved in their pathogenesis.

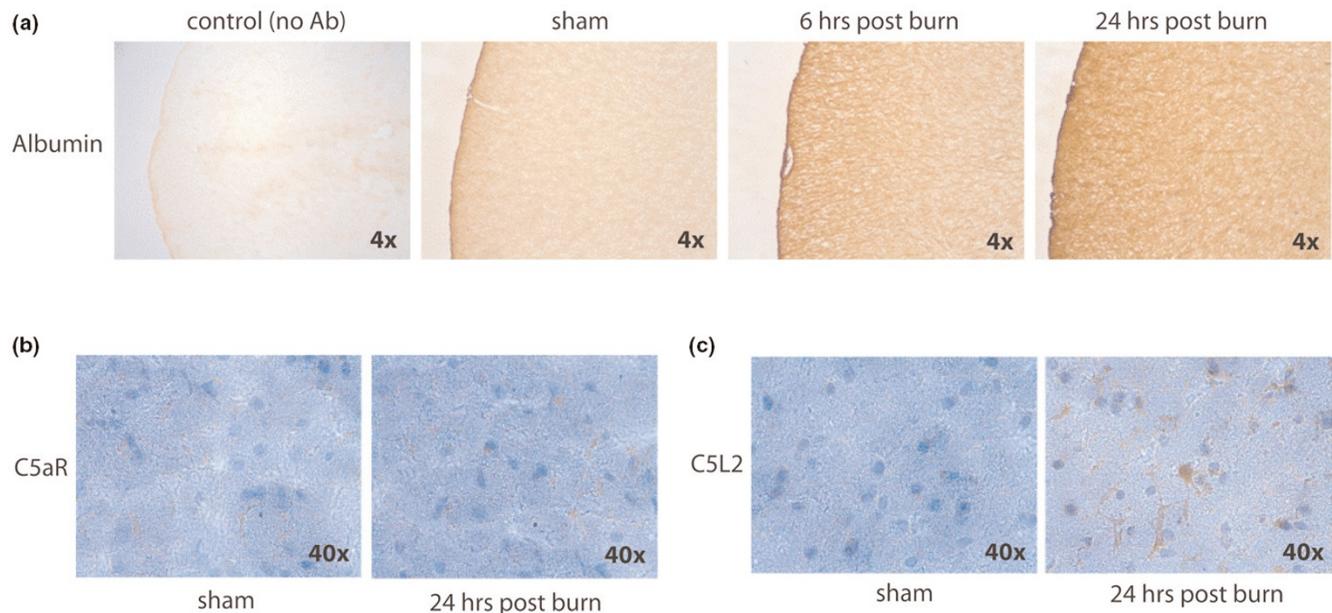
Breakdown of the blood–brain barrier and development of cerebral edema

Under physiological conditions, the blood–brain barrier (BBB) tightly regulates the molecules that enter the brain tissue. During the systemic inflammatory response syndrome, sepsis, or severe burn injury, however, this physical barrier between the systemic circulation and the cerebral parenchyma can be seriously compromised.

When peripheral tissues are exposed to severe burns, they release a plethora of proinflammatory mediators, cytotoxic proteases, reactive nitrogen species, and reactive oxygen species. These mediators then cause systemic reactions, such as fever [7,8], hypogeusia [9], hyperalgesia [10,11], severe burn-induced anorexia (wasting syndrome) [9,12], hormonal alterations of the hypothalamic–pituitary–adrenal axis, and changes of endogenous catecholamine levels [13,14]. All of these inflammatory changes attempt to restore equilibrium in the body. When the burn load is overwhelming, however, the systemic levels of released inflammatory mediators become

BBB = blood–brain barrier; IL = interleukin; NO = nitric oxide; TNF = tumor necrosis factor.

Figure 1



Blood–brain barrier breakdown and complement C5a receptor expression in experimental burn injury. **(a)** Coronal sections of rat brains obtained as a function of time after experimental burn injury. Sections were then subjected to immunohistochemical staining for albumin. In the control slide, the primary antibody was omitted (no Ab) to ensure specific staining of the albumin antibody. Brain slides from sham animals (sham) were compared with brains obtained from burned rats. Note the progressive breakdown of the blood–brain barrier from 6 to 24 hours after burn injury resulting in increased cerebral accumulation of albumin. As a large systemic molecule, albumin can only cross the blood–brain barrier when this barricade is compromised. The present data are thus indicative of increasing blood–brain barrier collapse and subsequent development of cerebral edema. Coronal brain sections were obtained from sham animals and 24 hours after burn trauma, respectively, and were immunostained for **(b)** the C5a receptor (C5aR) and **(c)** the C5a-like receptor 2 (C5L2). Sections were then counterstained with Fast Blue. Areas depicted focus on the hippocampal area of the brain. Stained cells represent microglia. While there was no difference in the expression of C5aR between sham and burn rats, C5L2 expression was significantly upregulated in brains harvested from burnt animals in comparison with sham littermates. The complement system may play an important role in the development of burn-induced neuroinflammation. Slides were analyzed by light microscopy using fourfold (4x) and 40-fold (40x) magnification.

excessive and disproportionate with deleterious outcome [15]. The cerebral microvascular permeability is increased and enables previously blocked, large systemic molecules, such as albumin (Figure 1a), exudates, and numerous inflammatory cells to leak into the surrounding brain tissue.

These events cause subsequent neuronal damage [16] and cerebral edema [17,18], and can result in critically increased intracranial pressure [19]. The pathophysiological events leading to this severe inflammatory downward spiral are depicted in Figure 2. The extent of BBB leakage following severe burn seems to correlate with mortality in severe burn victims [5]. In the following sections, we illustrate the molecular mechanisms involved in BBB failure.

Subcellular immunological changes

Complement activation

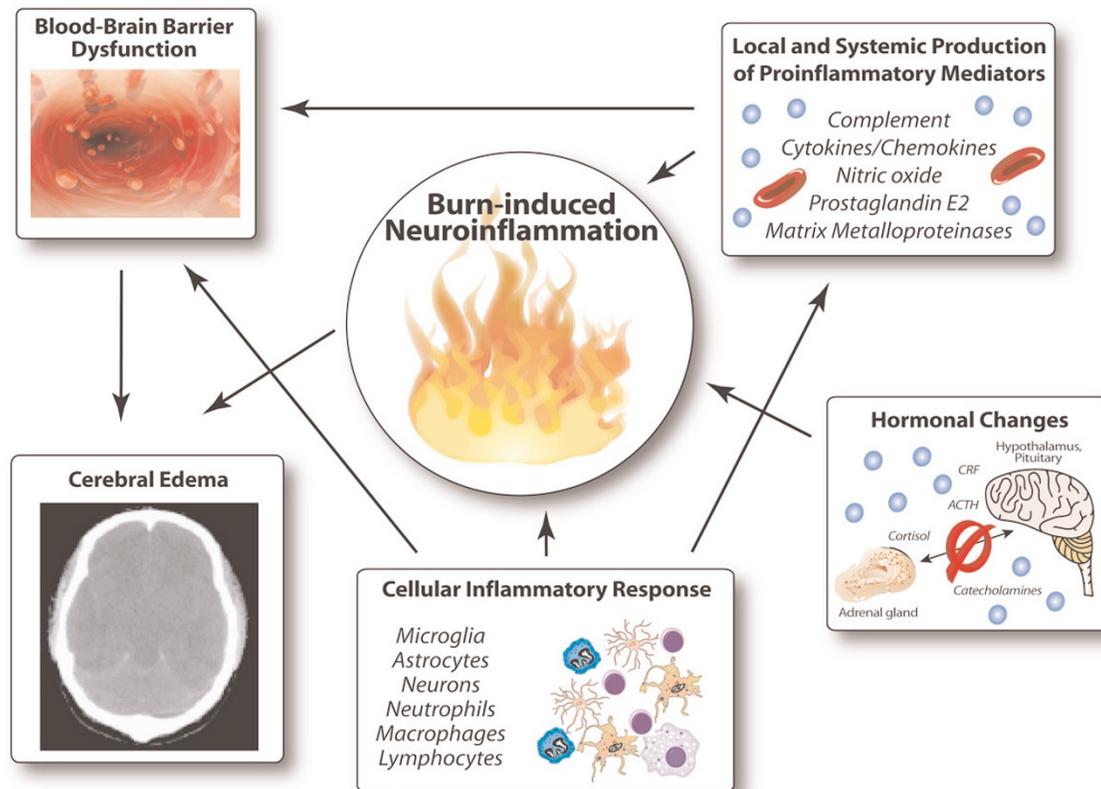
Activation of the complement system has been described following severe burns in experimental as well as patient settings [20,21]. While beneficial in moderation, overshooting activation of complement can become harmful to the host. In

fact, experimental burn trauma-induced secondary injury to the lungs [20] and burn-induced generation of the anaphylatoxin C5a could be linked to cardiac dysfunction, represented by significant reduction of left ventricular pressures and impaired sarcomere contractility [22]. In addition, robust complement activation has been described as a key event in the neuropathophysiology of traumatic brain injury and meningitis [23].

Surprisingly, there is extremely limited literature on the role of the complement system in neuroinflammation following burns. It seems reasonable, however, to assume that the complement cascade plays an important role in the pathophysiology of burn-induced neuroinflammation, since components of the complement system are being expressed and released by multiple sessile cerebral cell types.

In our laboratory, we found evidence of burn-induced modulation of the two C5a receptors (C5aR and C5L2) following a standardized rat model of full-thickness scald injury, in which 30% of the total body surface area is burnt. We compared

Figure 2



Pathophysiological events resulting in blood–brain barrier breakdown and development of cerebral edema following burn injury. Following major burn trauma, a robust systemic inflammatory response is triggered. Proinflammatory mediators are produced by various immune cells, resulting in breakdown of the blood–brain barrier, with subsequent activation of resident central nervous system cells, such as microglia and astrocytes, which respond with further production of inflammatory markers, cumulating in a massive neuroinflammatory response and subsequent life-threatening cerebral edema. In parallel, significant hormonal changes are triggered, resulting in a severe hypermetabolic state. CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone.

the expression of C5aR and C5L2 in the hippocampal areas of sham or burn animals (Flierl MA, Stahel PF, Touban BM, unpublished observations; Figure 1). While there seemed to be no change in the hippocampal expression of C5aR following burns, a significant upregulation of C5L2 was found 24 hours after burn trauma (Figure 1b,c). Contrary to earlier speculation, C5L2 has been recently identified as a functional receptor with a clearly proinflammatory role [24]. C5L2 may therefore contribute to the complement-mediated neuroinflammation after burns.

Cytokines and chemokines

Severe burn trauma induces rapid local production of proinflammatory cytokines by the affected tissues. Serum levels of TNF α , IL-1 β and IL-6 have all been reported to be elevated following severe burn trauma in humans and animals [25-28]. While serum concentrations of IL-6, IL-8 and IL-1 β correlate proportionally with the extent of the severe burn trauma, only serum IL-8 levels correlated positively with mortality [27,29].

TNF α , IL-1 β and IL-6 have all been demonstrated to *directly* induce a disruption of the BBB *in vitro* [30].

Recent studies in various animal models of neuroinflammation have confirmed breakdown of the BBB in a cytokine/chemokine-dependent manner [31-33]. Cytokines and chemokines are initially only produced at the burn site, but may become systemic and directly attack the BBB. In addition, severe burn injury significantly upregulates mRNA levels of TNF α , IL-1 β and intercellular adhesion molecule 1 in brain tissue as early as 3 hours post injury [26]. It is therefore important to recognize that severe burn trauma exposes the BBB to harmful proinflammatory mediators deriving from two different compartments: the brain and the systemic circulation. While, to date, there are no data available indicating what severity of burn injury is required to produce breakdown of the BBB in humans, most animal models cause severe burns on 60 to 70% of the body surface to induce BBB dysfunction [34,35].

Nitric oxide

Nitric oxide (NO) has multifaceted biological and immunological functions [36,37] and is biosynthesized by different isoforms of NO synthases localized in neurons, in endothelial cells, or in mitochondria [38]. In contrast, inducible NO synthase is expressed in all nucleated cells that generate large bursts of NO in response to immunological stimuli [39]. NO output by inducible NO synthase is generally associated with inflammatory conditions, such as hemorrhage, trauma, or severe burns [39,40]. Inhibition of inducible NO synthase reduces microvascular leakage after experimental severe burn trauma [41], and beneficial effects of inducible NO synthase blockade following severe burns have been reported [42].

There is considerable debate about whether plasma of urinary levels of nitrate and nitrite bear any predictive value influencing clinical decision-making in burn patients. While some studies report elevated levels of NO, nitrite, and nitrate and correlate NO levels on day 5 post burn with mortality [43-45], other studies describe significantly depressed plasmatic nitrite levels and elevated nitrate levels [46]. Reports about urinary nitrite and nitrate concentrations following burns also remain controversial [45-48]. The adverse effects of NO following severe burns may be mediated by interaction of NO with superoxide (O_2^-), resulting in formation of the highly toxic oxidant peroxynitrite [49]. Peroxynitrite then causes extensive tissue damage and edema formation [50,51]. Production of peroxynitrite has been described in organs remote to the site of severe burn injury, making it an important mediator of severe burn-induced multiple organ failure [52,53].

Unexpectedly, mRNA expression of inducible NO synthase in the hypothalamus is significantly decreased following thermal injury [54], and NO levels rapidly declined in the cerebral cortex following severe burns [55]. Hypotheses for this central/peripheral discrepancy include recruitment of NO from the brain towards the burn site, and/or a negative feedback loop blocking central NO because of its oxidative and free-radical deleterious effects [55].

Prostaglandin E₂ and matrix metalloproteinases

Peripheral severe burn injury induces cyclooxygenase-2 as well as microsomal-type prostaglandin E synthase in endothelial cells of the central nervous system, resulting in elevated levels of prostaglandin E₂ in the cerebrospinal fluid [56]. Elevation of prostaglandin E₂ levels in cerebrospinal fluids may therefore be involved in the pathogenesis of the central nervous system-mediated systemic reactions following severe burns. Ultimately, severe burn patients may benefit from administration of a cyclooxygenase-2-selective inhibitor in the treatment of central nervous system-mediated symptoms. Awareness of the increased risk of gastrointestinal bleeding following administration of cyclooxygenase-2-selective inhibitors, however, is important.

Matrix metalloproteinases have been recently identified as key players in the development of BBB dysfunction following severe burn injury [34,35]. When upregulated following severe burns, these proteases may contribute to the degradation and destruction of the basal lamina of the BBB.

Disturbance of hormonal stress response

Following severe burn injury, the body reacts with a general stress response [57]. After an initial ebb phase [12,58], a universal hypercatabolism occurs [57]. This hypermetabolism is, at least in part, mediated by catecholamines and correlates with the severity of injury [14]. Following severe burn, plasma catecholamines increase as much as 10-fold [59,60], resulting in hyperdynamic circulation [61]. In addition, levels of norepinephrine and dopamine increase in certain areas of the brain [12,58,62] and increased levels of catecholamines mobilize substrates from the body's fat and protein stores, leading to loss of lean body mass and muscular wasting [12]. Blockade of β -adrenergic receptors following severe burns therefore decreases thermogenesis, tachycardia, cardiac workload, and resting energy expenditure [63-65]. In severely burned children, treatment with the β -adrenoceptor blocker propranolol attenuated hypermetabolism and reversed muscle-protein catabolism [66,67].

Alterations in hypothalamic function due to severe burns have also been described [68]. More recent research confirmed disturbance of the hypothalamic-pituitary-adrenal axis in severely burned patients. Hypothalamic peptides and receptors of the corticotropin releasing factor family have been identified as putative mediators of severe burn-induced hypermetabolism [69,70]. Serum prolactin has been found to correlate with burn severity [29] and, further downstream, temporary adrenal insufficiency has been reported in the early stages of severe burn trauma [71], which was associated with higher mortality rates [72]. A study investigating the hypothalamic-pituitary-adrenal axis following thermal injury in children found a disrupted adrenocorticotrophic hormone-adrenal feedback loop [73].

Cellular changes

Neurons

There are no reports to date directly investigating the activation of microglia and glial scarring following severe burns. In a recent study, the peripheral axon caliber and the conduction velocity were severely impaired after experimental severe burn injury [74]. These morphological and functional deficits were observed at sites remote from the burn site. Axon caliber reduction and reduced neuronal conduction velocity following severe burns may therefore affect not only peripheral, but also central, neurons and may contribute to alterations of neuromuscular transmission and the development of limb and respiratory muscle weakness that often accompanies severe burns. Moreover, in burn-injured tissue, long-lasting activation of peripheral sensory neurons results in reorganization in the spinal cord [75]. Histologically, the

dorsal horn of the spinal cord shows decreased expression of μ -opioid receptors [76].

Nerve growth factor was detected recently in newly formed epithelial cells at wound edges [77]. This growth factor may not only assist in wound reorganization and healing, but may also trigger hypersensitivity to heat and mechanical stimuli following severe burns [78,79]. Nerve growth factor seems to increase the strength and distribution of afferent neuronal connections with the neurons of the dorsal horn [80], and thereby expands their receptive fields [81]. These findings indicate that central plasticity occurs in the spinal cord after peripheral severe burns.

Neutrophils and macrophages

Severe burn injuries activate neutrophils and macrophages [82]. Intracerebrally produced cytokines and chemokines chemoattract phagocytes via the BBB [26]. In addition, once the BBB is severely compromised, systemic phagocytes can enter freely into the brain perivascular space [83]. Activated phagocytes release their full inflammatory arsenal of proteases, reactive oxygen species, and reactive nitrogen species [84-86], exacerbating the neuroinflammatory response. The productive capacity of phagocytes for proinflammatory mediators is markedly enhanced following severe burns [82]. Macrophages display increased oxidative metabolism after thermal injury [85], and patients with severe burns demonstrate evidence of increased oxygen free radical activity [87]. Consequently, nonsurvivors of severe burn trauma display increased consumption of antioxidants when compared with survivors [87].

Neuropsychiatric effects and cognitive dysfunction

Neuropsychiatric effects

Severe burn trauma triggers significant electroencephalogram aberrations [88]. During initial cardiovascular stabilization, resuscitation, and pain relief, less obvious neuropsychiatric consequences may be frequently masked by sedative treatments. Neuroses, cognitive impairment, and behavioral consequences have all been described in the literature after severe burns [89,90]. During the initial phase after thermal injury, temporary amnesia may occur [91].

As mentioned above, NO levels are upregulated throughout the periphery following severe burn injury. In addition, NO has been shown to be an important biomolecule in the central nervous system, where neuronal NO synthases are widely present [92]. The putative role of NO as a neuropsychiatric neurotransmitter concerns long-term potentiation in the hippocampus and long-term depression in the cerebellum [93,94]. NO seems to be particularly involved in short-term memory and learning [92,95]. Biobehavioral tests confirmed the important role of NO in the acquisition and consolidation of memories [96,97]. Rapid and significant decreases of cerebral NO levels were recently found to account for the

behavioral changes occurring in rats [55]. It remains to be seen whether alterations of intracerebral NO metabolism may alleviate severe burn-induced cognitive impairment.

Cognitive dysfunction

Approximately one-third of burn victims show evidence of physical, psychiatric, or alcohol-related problems, predisposing them to injury [98]. During the critical resuscitative stage immediately following burn injury, patients frequently display cognitive changes such as extreme drowsiness, confusion, disorientation, delirium, and psychotic reactions [99]. During the acute phase of recovery and restorative care, symptoms of depression, anxiety, sleep disturbance, and premorbid psychopathology are common [100]. Following discharge, patients may develop symptoms of depression or post-traumatic stress disorder, which can develop anywhere from 1 month after burn trauma to 2 years after the initial burn [99,101]. More than 50% of patients with burn injuries report moderate to severe depression symptoms early in their hospitalizations, and almost 50% retain these symptoms 2 years after injury [102,103]. Interestingly, the extent of burn trauma does not predict the psychologic problems after burn trauma [102-104]. One year after burn trauma, approximately 20% of patients meet the diagnostic criteria for post-traumatic stress disorder [105].

Dysfunctional beliefs such as fear-avoidance or neuroticism have been described as long-term sequelae after burn trauma [106]. Sleep disorders have also been described as long-term sequelae of burn trauma [107]. A multidisciplinary team approach seems to be key to a successful management and long-term reintegration of the burn patient.

Impact of the immunopathophysiology on burn management

Advances in burn care have resulted in significant reduction of mortality rates over the past 50 years [108-110]. In particular, early and aggressive excision of the burn wound has had the greatest impact on burn patient morbidity and mortality by reducing the incidence of wound sepsis, hypercatabolism, numbers of operations, and hospital lengths of stay [111-114]. The current treatment guidelines therefore recommend routine and aggressive debridement of severe burn wounds at the first medical facility available [115]. Even during infectious complications following severe burns, the cornerstone of treatment remains early, aggressive, and definitive surgical debridement – while antibiotics are only considered important adjuncts to management [116]. Subsequent skin grafting is usually achieved with autologous or allogenic skin or biosynthetic dermal substitutes [117].

It is conceivable that the unquestionable benefit of early and aggressive excision of the burn wound is closely related to the pathophysiological changes described above. When the burn load is excessive, the local inflammatory response initiated by the injured peripheral tissues can spill over into

the systemic circulation and result in the aforementioned inflammatory vicious cycle. The ensuing downward spiral may thus be disrupted early by aggressive initial debridement and may significantly reduce the systemic inflammatory burden with improved end-organ function and reduced morbidity and mortality. Early excision of full thickness burns is also associated with attenuation of burn-induced hypermetabolism [118-120].

Currently, bench-to-bedside transfer of several promising immunomodulatory treatment strategies – such as immunonutrition, administration of recombinant human activated protein C, or topical immunosuppressants – are under investigation, as discussed in detail elsewhere [121]. As a result, a recent report called for further translation of ‘excellent animal work into the human arena’ to advance care of the severely burnt patient [122].

Conclusion

Severe burn-induced neuroinflammation is a highly complex and intricate entity. Optimal management of the severely burned patient can only be achieved if the treating critical-care personnel are intimately familiar with the systemic and cerebral pathophysiology following severe burn trauma, and adjust their treatment modalities accordingly. While collapse of barriers in the lungs, kidneys, or liver is usually recognized by simple laboratory parameters and is treated as part of the severe burn management, burn-induced neuroinflammation evolves over time and thus cannot be detected on initial computerized tomography imaging evaluation. If the treating physician fails to appreciate the complex cerebral inflammatory events following burns, the patient may be cleared prematurely for surgical interventions, which can result in a potentially detrimental iatrogenic second hit. The treating physician therefore needs to maintain a high index of suspicion for this challenging entity. While some of the molecular events involved are well understood, many unanswered questions remain, which need to be addressed in experimental and clinical studies in order to advance care of the critically ill burn patient.

Competing interests

The authors declare that they have no competing interests.

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