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Extracorporeal Blood Purification in Burns: For Whom, Why, and How?

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Key Messages

- Patients with serious burn injuries, >30% of the total body surface, require immediate specialized care in order to minimize morbidity and mortality.
- Burn injury induces overall activation of the immuno-inflammatory system, resulting in suppressed immune function and increased susceptibility to infection.
- Extracorporeal blood purification (BP) could be of interest in this population to mitigate immune dysregulation, prevent secondary complications, and potentially reduce morbidity and mortality.
- Current understanding of sepsis pathophysiology, acute pancreatitis, and ischemia/reperfusion lesions following cardiac arrest should provide insights into the processes related to the inflammatory state seen in burn patients. All these clinical settings may share similar potential new therapeutic pathways.
- Lack of morbidity/mortality improvement with extracorporeal BP in randomized controlled trials in sepsis may possibly be explained by significant heterogeneity in terms of indications, timing of initiation, and patient populations.
- Limited data is available although there is a strong rationale to assess extracorporeal BP techniques in burn patients.
- Further research is needed in order to make recommendations regarding BP in burn patients.

Keywords
Burn · Extracorporeal blood purification · Hemoperfusion · Inflammation

Abstract
Patients with serious thermal burn injuries require immediate and specialized care in order to minimize morbidity and mortality. Optimal fluid resuscitation, nutritional support, pulmonary care, burn wound care, and infection control practices represent key aspects of patient care in burn centers. When severely burned, the patient usually presents a systemic inflammatory response syndrome, soon balanced by a counter anti-inflammatory response syndrome. These may lead to immune dysregulation/exhaustion favoring infectious complications that dramatically impair the prognosis of burn patients. This narrative review provides an overview of the main concepts, current understanding, and potential applications of extracorporeal blood purification techniques for burn patient management. Current understanding of burn patients' immune responses is reported. Hypotheses and data on the potential value of immunoregulation are reviewed. Finally, how extracorporeal blood purification may be of interest in this specific population is discussed.

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Introduction

Burns are among the most common and devastating forms of trauma. Patients with serious burn injuries require immediate and specialized care in order to minimize morbidity and mortality [1]. The survival rate for burn patients has improved substantially in the past few decades due to advances in medical care provided in specialized burn centers. Optimal fluid resuscitation, nutritional support, respiratory care, burn wound care, and infection control practices represent key aspects of patient care in burn centers.

There is always a local inflammatory response to trauma. In severe cases, including burns, the patient also presents a systemic inflammatory response syndrome (SIRS) that is caused by hormonal, metabolic, and immunological mediators and is associated with a hemodynamic response [2]. Significant burn injuries also induce a state of immunosuppression favoring infectious complications that dramatically impair the prognosis of burn patients. Together, SIRS, sepsis, and multiple-organ dysfunction syndrome remain major determinants of morbidity and mortality [3, 4]. As a result, further efforts in the pathophysiology understanding, treatment, and regulation of immune response may hold some promise for the future of burn treatment. The aim of this narrative review was to provide an overview of the main concepts, current understanding, and potential applications of extracorporeal blood purification (BP) techniques for burn patient management.

What Is the Current Knowledge on the Inflammatory State of Burn Patients?

Our current understanding of burn wounds includes three zones of injury: zone of coagulation, zone of stasis, and zone of hyperemia [5]. Destroyed tissues (coagulation zone) are surrounded by an area characterized by inflammation and low levels of perfusion (zone of stasis), which is itself surrounded by an area with preserved microvascular perfusion (zone of hyperemia). The zone of stasis usually progresses to necrosis within the first 48 h following burn injury, which results in the initial burn expansion in both area and depth.

Three main pathophysiological pathways leading to microvascular dysfunction are associated with burn-related disorders: vessel thrombosis resulting from vascular damage mediated by inflammatory mediators such as histamine, bradykinin, prostaglandins, leukotrienes, vasopressors, platelet activation products, and complement [5]; the release of proinflammatory mediators from sequestered leukocytes in injured tissues that cause microvascular damage [6]; and an increased expression of proapoptotic factors including Bax, Bcl-xl, and caspase-3 activity, partly due to the action of tumor necrosis factor (TNF)-α [5].

The products released by burned tissues result in a biphasic proinflammatory and then anti-inflammatory response syndrome. This release of cytokines and other inflammatory mediators at the site of injury is known to mediate a systemic effect once the burn reaches 30% of total body surface area (TBSA) [7]. Then, the imbalance between the pro- and anti-inflammatory response syndrome occurs with an immune dysregulation and patient vulnerability to a second hit such as sepsis.

The Systemic Proinflammatory Response

Innate Immunity Activation

Burns are first associated with the activation of innate immunity. At the molecular level, the initiation of general inflammation and SIRS broadly depends on damage-associated molecular pattern (DAMP) and pathogen-associated molecular pattern (PAMP) [8].

DAMPs are released by injured tissues throughout trauma, surgical procedure-related trauma, or acute pancreatitis, whereas PAMPs are associated with bacterial or viral infection and toxic shock syndrome. Both DAMPs and PAMPs are also released from burn-injured tissue and transferred to systemic circulation when the burn area is extensive. DAMPs released after tissue injury activate toll-like receptors (TLRs) and thus play a major role in the activation of innate immunity. Data suggest that TLRs and TLR-mediated responses are up-regulated after a burn injury [9].

Cellular Response

As in severe trauma, neutrophils become primed by chemoattractants in the injured tissue and by exposure to circulating cytokines. They accumulate not only in the injured tissue but also in the systemic circulation. These neutrophils are protective against infection; however, they release enzymes (elastase and myeloperoxidase) and are capable of oxidative burst activity, which may cause damage to uninjured tissue and can lead to remote organ dysfunction. Owing to their activation, stimulation, and excessive accumulation in injured tissue, neutrophil activity is impaired.

Additionally, in the injured area, monocytes and endothelial cells release proinflammatory cytokines, the

main ones being interleukin (IL) -1-β, IL-6, IL-8, TNF-α, and interferon γ [10]. Another central cellular element is the differentiation of monocytes into macrophages. These are major producers of proinflammatory mediators, reactive nitrogen intermediates, IL-6, and TNF-α [11]. Moreover, burn injury seems to increase the capacity of macrophages to produce these mediators [12]. Dysregulation of macrophage activity leading to increased release of proinflammatory factors, also known as macrophage hyperactivity, appears to be of fundamental importance in the development of postburn immune dysfunction [13].

Cytokine Release

Burn injury results in a prolonged and profound hypermetabolism involving increased production of proinflammatory cytokines as well as the release of reactive oxygen species. These reactive oxygen species are harmful and are involved in general inflammation, immunosuppression, infection and sepsis, tissue damage, and multiple organ failure. Clinical response to burn may therefore also depend on the balance between production of free radicals and their detoxification [14]. Burn-related upregulation of the inducible NO synthase pathway may produce peripheral vasodilatation, upregulate the nuclear transcription factor-κB (NF-κB), and promote transcription and translation of numerous inflammatory cytokines [15, 16].

Enhanced catabolism and metabolism, both having a significant impact on morbidity and mortality, are associated with high levels of pro- and anti-inflammatory cytokines in burns [17, 18]. The inflammatory and hypermetabolic responses have been shown to begin early, within the first 24 h after the burn injury, and to be burn-size dependent [19, 20]. The first cytokines released after trauma are TNF-α and IL-1 [21]; these stimulate many immunological cells and are able to induce secretion of other proinflammatory cytokines such as IL-6 and IL-8, and the anti-inflammatory cytokine IL-10 [22]. Early measurements of the circulating TNF-α/IL-10 ratio may represent an interesting biomarker of burn injury severity, possibly predictive of the risk of hypersusceptibility to subsequent infections [23, 24].

Among proinflammatory cytokines, only IL-6 has constantly been shown to be elevated systemically after burn injury. In experimental animal models of third-degree burns >20% TBSA, serum IL-6 levels peaked during the first hours after injury and were directly related to the size of the burn injury area [25]. The secretion of IL-6 correlates with the magnitude of the trauma, the duration of surgery, and the risk of postoperative complications [26]. Furthermore, clinical and experimental studies have reported a significant increase in IL-6 production after burn injury and sepsis that was correlated with suppressed cell-mediated immunity and increased mortality [27, 28]. Interestingly, although IL-6 is a proinflammatory cytokine in the early hours following the injury, it also induces the production of prostaglandin E2, suggesting that it has anti-inflammatory and immunosuppressive effects as well [29, 30].

The Counter Anti-Inflammatory Response Syndrome

The counter anti-inflammatory response syndrome depends on T helper cells (Th-2) and three key mediators (IL-4, IL-10, and TGF). Recent findings have also identified a role played by other regulatory T-cell populations in suppressing T-cell immunity such as natural killer T-cells (NKT) and gamma delta T-cells [31]. Patients with TBSA >30% had different reactions of burn trauma compared to those with TBSA <30% and developed an extended inflammatory response, which covers not only proinflammatory aspects as described previously but also immunoinhibitory aspects [32]. This immune dysregulation may lead to impaired immunoreactivity and increase incidence of septic complications and death. An increased production of IL-10 has been described following major injury with an increased occurrence of infection and poorer resistance to this [33].

In conclusion, the inflammatory state of severe burn patients could be summarized in two phases. The first one is a major proinflammatory response and may cause remote organ dysfunction. The second one is a counter anti-inflammatory response syndrome that may make patients and their exhausted and dysregulated immune system vulnerable to a potential second hit such as sepsis (shown in Fig. 1).

Why Does Extracorporeal BP Make Sense for Severe Burn Injury?

Sir William Osler stated in 1904 in *The Evolution of Modern Medicine* that "except on few occasions, the patient appears to die from the body's response to infection rather than from it" [34]. Our current understanding of sepsis, acute pancreatitis, and ischemia/reperfusion injuries following cardiac arrest may help provide some insight regarding the processes related to the inflammatory state seen in burn patients.

Cytokine biosynthesis runs through two major signaling pathways: p38 mitogen-activated protein kinase (p38

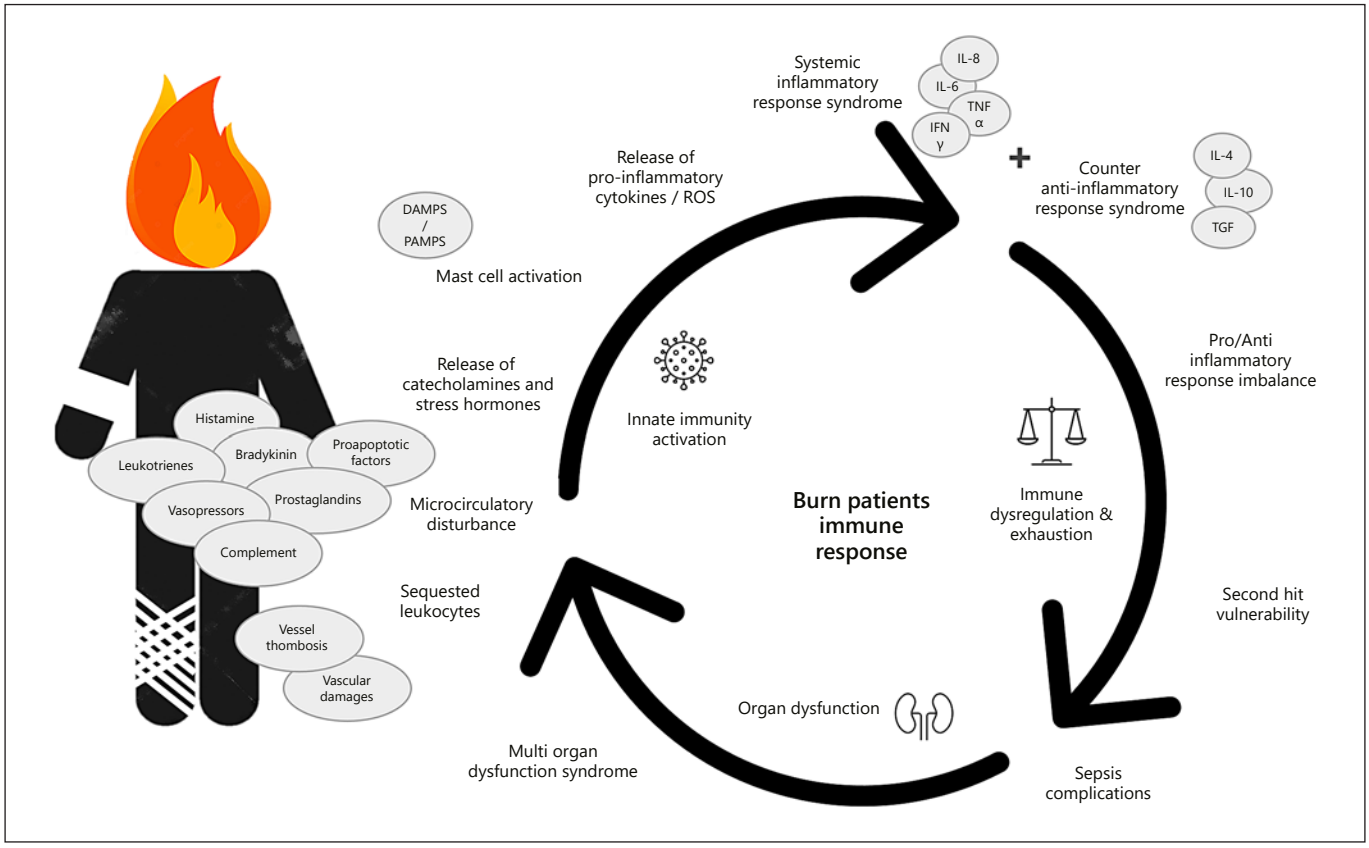

Fig. 1. Burn patients' immune response.

MAPK) and NF-κB. Data suggest that p38 MAPK activation is one aspect of the signaling cascade that culminates in post-burn secretion of TNF-α [35]. A study shows that inhibition of p38 mitogen-activated protein kinase largely improves resulting vascular dysfunction [5]. Other studies enhanced that continuous BP could potentially downregulate the p38 MAPK signaling pathway, suppress inducible nitric oxide synthase expression, reduce the serum levels of nitric oxide and TNF-α, and thus improve symptoms of multiple organ failure [36, 37].

Down regulation or control of this dysregulated immune response could be the next target for future practice to mitigate inflammation-related complications, organ dysfunction, morbidity, and mortality. This has pushed physicians and researchers to focus on the potential value of immunomodulation for burn patients, either by the topical delivery of (anti-TNFα)-hyaluronic acid conjugates or systemic use of immunomodulation of macrophage hyperactivity in animal models [38–41]. One could therefore consider that a nonselective approach using extracorporeal BP could be an attractive adjuvant treatment option; BP could help to restore a better balance of pro-inflammatory and anti-inflammatory state homeostasis until the pathophysiology of the inflammatory response related to burns is more deeply understood [42, 43].

Most BP techniques focus on the removal of cytokines and/or endotoxins (or PAMPs) that trigger the immuno-inflammatory cascade. Interestingly, some renal replacement therapy membranes, exhibiting enhanced adsorptive properties, combine cytokine and endotoxin removal with renal replacement function and antithrombogenic properties [44].

Mostly described in sepsis, extracorporeal BP techniques may be proposed in acute pancreatitis, trauma, but also burns [44]. As stated above, regardless of the source of inflammation, the human response may represent a "common pathway", with SIRS and an immune dysregulation that could lead to better patient care by modulating cytokine levels and that could reduce their harm [42].

One way to prevent this dysregulated immune response is based on the "peak concentration hypothesis". It states that by reducing total cytokine levels in the early

proinflammatory phase, subsequent organ failure and mortality may be prevented [45]. One could consider that early initiation of BP, being continuous and unselective, might be beneficial in cutting the peaks of the concentrations of both pro- and anti-inflammatory mediators, and help to restore immune homeostasis.

In contrast, a second hypothesis, called "the threshold immunomodulation theory", describes the potential nonselective benefit of BP by removing cytokines from the blood but also cytokines from the interstitium and tissues because of a concentration gradient until a new equilibrium is achieved. The cascade of exaggerated inflammation might therefore be stopped and organ damage could possibly be prevented [46].

In the third so-called "mediator delivery hypothesis", the potential of high replacement volumes to increase lymphatic flow is proposed, as it may help to transport and deliver cytokines to the blood compartment where they can be removed using BP techniques [47].

BP has also been suggested to act at the inflammatory cell level, to help to restore immune function of monocytes, neutrophils, or lymphocytes regulation, either through their direct removal or through an immune cell reprograming (modulation of surface markers expression, improvement of antigen-presenting capability, or adjustment of apoptosis) [48]. Several studies have recently supported this new "system reprogramming" theory [49, 50]. For instance, it has been reported that polymyxin-B hemoadsorption may increase the expression of leukocyte surface markers such as HLA-DR even if the mechanisms by which it happens remain unknown [49]. This new "cellular level" theory effect of BP, which may help to restore immune response, may conduct to reconsider the timing and indications of BP.

How Could BP Techniques Be of Interest in Severe Burn Patients?

The current literature on BP is dominated by studies including septic patients, with an interest in BP in the early phase of septic shock. The two most recent Surviving Sepsis Campaign guidelines could not make any strong recommendations regarding the use of these BP techniques in sepsis since the evidence, either in favor or against BP, is lacking [51, 52].

For example, the EUPHRATES randomized controlled trial evaluated polymyxin-B hemoperfusion in septic patients and included 450 adults with septic shock and high endotoxin activity [53]. Overall, the intervention was not effective in reducing mortality, although a post hoc analysis did suggest a survival benefit of polymyxin-B hemoperfusion in patients who experienced an endotoxin activity between 0.6 and 0.89 [54].

In this research area, many aspects remain to be fully elucidated; for instance, it is not precisely known how these therapies interfere with sepsis pathophysiology, which patients would benefit the most from BP, when to use these techniques, and what to exactly remove [45, 55, 56]. Our better understanding of sepsis-induced immune responses and associated treatments could benefit the burn population of critically ill patients. Immunomodulation with extracorporeal BP techniques could therefore be proposed in burn patients, particularly in the setting of refractory shock and organ dysfunctions. Burn patients do indeed commonly present with acute kidney injury (AKI), the frequency of which is reported to be as high as 30%, and related mortality as high as 80% [57]. Chung et al. [58] recently reported in several cohorts that the application of renal replacement therapy in adult patients with severe burns and AKI was associated with a decrease in morbidity and mortality [59]. Animal studies in burn models also exhibit promising results with a significant removal of IL-1, IL-6, IL-10, and myoglobin by the Cytosorb™ hemoadsorptive column when performed for 6 h sessions during a 3 day period, even if no significant systemic or pulmonary reductions of cytokines were found [60].

You et al. [61] have proposed a protocol of high-volume hemofiltration therapy for 3 days within 3 days after the burn injury. The "Randomized Controlled Evaluation of Hemofiltration in Adult Burn Patients with Septic Shock and Acute Renal Failure" (RESCUE) trial is ongoing and will address the potential utility of high-volume hemofiltration in the setting of delayed complication of burn injury [62]. Zhang et al. [43] recently reported a meta-analysis of current data regarding the efficacy and safety of BP in the burn population. Nevertheless, the effects and potential benefit of BP techniques in burn patients are still based on scarce data and are pending on research and data as stated by Linden et al. [42].

To date, no strong recommendation can be made regarding the timing of BP initiation, the modality to use, monitoring, or the duration of therapy. From a theoretical point of view, early initiation of BP, within the first hours after the insult is likely to be associated with the best clinical response; at this point a significant amount of inflammatory mediators are, or are about to be, released in the blood. This early initiation may therefore mitigate the inflammatory response and potentially prevent remote organ dys-

function. Interestingly, in burns, as opposed to sepsis, the precise moment of the injury is known, which may facilitate the standardization of initiation timing. A recent study by Chung et al. [58] reported that early intervention with continuous high-volume hemofiltration may reduce the incidence of sepsis, septic shock, and organ failure in patients with burns ≥50% TBSA and may improve the survival of patients with burns ≥80% TBSA [61]. Several other cases and studies were reported and demonstrate excellent adsorption rates for inflammatory cytokines, hemodynamic stabilization, and a potential value to prevent organ failure in critically ill burn patients [63].

The question of which parameters could be used as triggers for BP initiation remains largely unanswered. Further studies should be conducted to assess potential candidate biomarkers such as IL-6 or procalcitonin. Similarly, other markers could help identify a state of immunosuppression and serve as "late" biomarkers; a candidate biomarker for this could be mHLA-DR [64].

The modality of BP and the duration of therapy have been poorly studied in burn patients. Clinical experience with BP adsorptive devices for burn patients are limited to Coupled Plasma Filtration Adsorption, Jafron HA, or CytoSorb® cartridges which are all nonselective extracorporeal cytokine adsorbers [65, 66]. Hemoperfusion devices targeting cytokine removal and implemented early after burn trauma are the most likely to exhibit clinical efficacy.

Finally, little is known about therapy monitoring and endpoints assessing the technique's efficacy. Evaluation is currently done using the clinical response in terms of improvement of hemodynamic or respiratory parameters. Future clinical studies should therefore consider the evolution of candidate biomarkers and evaluate which ones can be considered to monitor therapy monitoring.

One should note that, as opposed to sepsis, in severe burn injuries the insult seems less heterogenous, the timing is well known, and patients are generally rapidly referred to a specialized center. Therefore, early or late extracorporeal BP and its modality could be considered more accurately and potentially be initiated in a homogenous burn population that may help investigators to rapidly design interesting trials.

Conclusion

Burn injury induces overall activation of the entire immuno-inflammatory system, resulting in suppressed immune function and increased susceptibility to infections. Extracorporeal BP could be of interest in this population to mitigate immune dysregulation, prevent secondary complications, and potentially decrease morbidity and mortality.

Current understanding of sepsis pathophysiology, acute pancreatitis, or ischemia/reperfusion injuries following cardiac arrest might provide insights into processes related to the inflammatory state seen in burn patients. All these clinical situations may benefit from the same innovative immunomodulatory treatments such as BP. Despite promising clinical data and trials, further investigations in both animal models and human clinical studies (including large prospective studies) are required to further elucidate the benefits of these therapies in severe burn injuries.

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Conflict of Interest Statement

Paul Abraham has no conflict of interest. Celine Monard has received speaker honoraria from Fresenius Medical Care and bioMerieux. Thomas Rimmelé has received speaker and/or consulting honoraria from Fresenius Medical Care, Baxter Healthcare Corp, Biomérieux, Jafron, Medtronics, Nikkiso, and B. Braun. Antoine Schneider has received speaker and/or consulting honoraria from Fresenius Medical Care, CytoSorbents SA, Jafron, Medtronics, and B. Braun Avitum.

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