

Pathophysiologic Similarities between Burn Injury Triggered Systemic Inflammatory Response Syndrome (SIRS) and COVID: Therapeutic Implications from Cytokines and Cells to Hospital Beds

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Abstract

Erosion of endothelial surface, disruption of endothelial glycocalyx and hyperinduction of inflammasome complexes are some of the main events taking place in early stages of COVID. Shedding of endothelial glycocalyx is also an important pathophysiologic finding in burn injury. It has also been shown that NLRP3 inflammasome is pivotal in activation of proinflammatory cascades triggered by burn injury which results in propagation to burn Systemic Inflammatory Response Syndrome (SIRS). Disruption of physiologic antithrombotic state of intravascular compartment is a hallmark of COVID. Complement activation especially mannose binding lectin pathway seems to have pivotal role in complement triggered inflammation and thrombotic state. This pathway is also implicated in burn injury triggered Systemic Inflammatory Response Syndrome (SIRS) as part of an innate immunity. Many pathophysiologic aspects of burn SIRS and sepsis share some important characteristics with those of COVID. Therefore, several dimensions of burn management should be implicated and investigated in the treatment of COVID.

Keywords: Systemic inflammatory response syndrome; COVID; Cytokines; Ventilation; Circulation

Introduction

From the days of uncertainty of COVID induced cellular and paracrine events and thus treatment strategies, published literature now has a substantial amount of data on how COVID affects multiple organs and systems at the same time. It is now accepted with reliable level of evidence that COVID produces both direct and indirect involvement of endothelium throughout body thus resulting in diverse clinical presentations and outcomes. Patients already having comorbidities affecting endothelium, e.g. diabetes, metabolic syndrome, obesity, smoking, etc., present even worse prognosis and this proves the pivot role of endothelial involvement in COVID.

Despite main parameters of treatment of COVID have been established, still different centers and different countries might embrace significantly different approaches. Given the ever increasing amount of data on endothelial involvement in COVID, therapeutic approaches might be adjusted from this point of view. Although it has not been reported directly, burn injury triggered systemic inflammatory response syndrome (SIRS) has similar pathophysiologic aspects with those of COVID presents. In this, I tried to summarize current evidence on similarities between burn injury triggered SIRS and COVID, related clinical implications and propose therapeutic approaches.

Literature Review

Pathophysiologic similarities between COVID and burn injury

Although vascular endothelial cells are not direct targets for SARS-CoV-2, multisystem involvement seen in COVID with variable clinical presentations reflects widespread endothelial inflammation. Erosion of endothelial surface, disruption of endothelial glycocalyx together with increased levels of main proinflammatory cytokines (e.g. IL-6 and TNF- α) and hyperinduction of inflammasome complexes, e.g. NLRP3, are some of the main events taking place in early stages of COVID [1]. Shedding of endothelial glycocalyx is also an important pathophysiologic finding in burn injury [2]. NLRP3 inflammasome has been shown to be responsible in release of many proinflammatory cytokines in various disease states. Both external agents, e.g. pathogenic microorganisms, and endogenous factors might activate this pathway. NLRP3 is also chronically activated in obesity, diabetes and metabolic syndrome and plays central role in propagation of these metabolic diseases [3]. This seems to be a major pathophysiologic factor in worse prognosis of COVID patients having these metabolic diseases. It has also been shown that NLRP3 is pivotal in activation of proinflammatory cascades triggered by burn injury which results in propagation to burn systemic inflammatory response syndrome (SIRS) [4]. This inflammasome is known to exert central role in leading to inflammation via IL-1 β and then other subsequent proinflammatory mediators, e.g. IL-6, IL-18 and TNF- α [5].

Disruption of physiologic antithrombotic state of intravascular compartment is a hallmark of COVID. Especially cardiopulmonary effects of the disease are triggered by prothrombotic state and widespread endothelial inflammation. Complement activation with

various pathways plays important role in hypercoagulative state and platelet activation. Especially mannose binding lectin pathway seems to have pivotal role in complement triggered inflammation and thrombotic state [6]. This pathway is also implicated in burn injury triggered systemic inflammatory response syndrome (SIRS) as part of an innate immunity [7]. Activated platelets aggravate inflammatory responses through their interactions with monocyte-macrophage system and neutrophils. The importance and interrelated nature of endothelial injury, platelet activation, increase in proinflammatory cytokines, i.e. cytokine storm and resultant blood viscosity explains most of the pathophysiologic processes of COVID take place in intravascular space. Since the lungs comprise a substantial amount of capillary network, it is no surprise that they are the top target for COVID. These microvascular effects of COVID have also been shown to last even after symptomatic relief and negative replicative tests [8]. Pulmonary, cardiac, hepatic and renal sequelae of COVID seem to be mainly related to widespread microvascular involvement and subsequent fibrotic cascades due to epithelial mesenchymal transition. Similar pneumonia like involvement and subsequent ARDS and Acute Lung Injury (ALI) are well known clinical presentations of burn SIRS and sepsis [9].

Vascular smooth muscle cells are direct targets for SARS-CoV-2 and vasoactive responses are also impaired in COVID [10]. Significant levels of complement induced inflammation of endothelial cells and direct viral infection of vascular smooth muscle cells impair endothelial-smooth muscle-pericyte crosstalk and these results in a vasoconstrictive “hypertonic” state in COVID together with propensity to extravasation in later stages of disease [11]. Especially in clinical states with already diminished levels of vasodilatory capacity of vessels (e.g. diabetes, metabolic syndrome, and smoking), the deleterious effects of “COVID Rheology” become even worse.

Many of these summarized cellular and paracrine events are very well documented in literature. One of the striking points is these pathophysiologic events are similar or identical at many points to the ones triggered by burn injury. In burn injuries involving large enough percentage of total body surface area to start Systemic Inflammatory Response Syndrome (SIRS), increased vascular permeability, propensity to thrombotic events, and decrease in cardiac, renal and hepatic functions are seen. The similarities between immune responses and pathophysiologic events of these two different clinical states should be considered together. Here I would like to suggest that some of the well-established parameters of burn treatment should be emphasized also in the treatment of COVID.

Therapeutic proposals

Most of the ongoing efforts and published literature to treat COVID, use or recommend various agents (e.g. drugs, convalescent plasma, cell therapies, etc.) directed to decrease viral replication; immunomodulation or trigger antibody mediated immune responses. Besides targeting viral replication and inflammation with direct agents, supportive treatment modifications targeting rheological and inflammatory effects due to endothelial involvement seems to be pivotal in the treatment of COVID. Many pathophysiologic aspects of burn SIRS and sepsis share some important characteristics with those of COVID. Therefore, several dimensions of burn management should be implicated and investigated in the treatment of COVID.

Maintenance of intravascular volume and antithrombotic state

Fluid therapy is one of the mainstay dimensions in management of major burns. Loss of considerable amount of skin barrier results in continuous fluid and electrolyte loss. Loss of endothelial glycocalyx is another hallmark of burn injury [12]. This loss results in a hypercoagulable state together with septic complications. A similar rheologic state is also seen in COVID and fluid management of COVID patients should be managed for each patient. Although overhydration can aggravate water and electrolyte leakage to interstitial space, hyperviscosity seen in COVID proves early fluid resuscitation and replacement is crucial to treat hyperinflammatory state since these two pathologic phenomena creates a vicious cycle. Increasing vascular tone with increasing severity of disease leads to biomechanical changes of vascular bed. During the short and rapid evolution of COVID treatment, attention has been paid to anticoagulant and antiaggregant agents to prevent this hypercoagulable state [13]. But this approach might be insufficient in a dehydrated patient. Limited oral intake due to loss of appetite and worsening general condition leads to dehydration in most of the COVID patients, e.g. geriatric patients. Early parenteral hydration of COVID patients, either in hospitalized or even in outpatient basis, might decrease the number of patients who eventually becomes hospitalized and the ones needed to be transferred to ICUs. Use of Fresh Frozen Plasma (FFP) and monitorization of extravascular lung water have been shown to be useful tools in fluid management of burn patients and these tools can be used in wider scale in the treatment of COVID [14,15]. Still there is no clear guideline advocating early fluid resuscitation adjusted individually for each patient in the treatment of COVID.

Maintenance of optimal body temperature

Increase in core body temperature is one of the hallmark evolutionary responses to viral infections. Although hyperthermia can have deleterious effects on central nervous system and gonadal tissues especially in pediatric patients. Since the majority of COVID patients are adults, empiric and liberal use of antipyretic agents can curb the defensive nature of fever response [16]. During early days of pandemic, use of NSAIDs and paracetamol had been both advocated and discussed. Besides widespread use of paracetamol and nonselective NSAIDs, suppressing fever response should be questioned.

Increasing body temperature also has vasodilatory effects which might be beneficial in COVID patients since a vasoconstrictive environment is created through impaired crosstalk between endothelial cells, vascular smooth muscle and pericytes. Selective COX2 inhibitor celecoxib seems to be a viable option suited to be used in COVID since it does not hamper fundamental immune cascades related with cyclooxygenase pathway, but alleviates exaggerated immune response centered around COX2. There is a need for randomized controlled studies regarding optimal use of antipyretics and optimal body temperature to be maintained during treatment of COVID.

Maintenance of nutritional status

Intestinal inflammation and increased intestinal permeability is one of the most critical pathophysiologic events seen in burn injury triggered systemic inflammatory response syndrome (SIRS). Bacterial translocation from intestinal flora through portal system is a well-

known pathophysiologic factor leading to sepsis and myocardial depression in burn injury. Once it is triggered, this process becomes a positive feedback increasing severity of systemic inflammation through various molecular patterns (e.g. lipopolysaccharides), decreasing splanchnic circulation via vasoconstriction and resultant intestinal ischemia only increases severity of bacterial translocation. It has been shown that COVID also involves intestinal system via both direct cytotoxicity and ischemia due to vasoconstriction. In COVID patients, there is a lack of emphasizing importance of nutrition. Loss of appetite diminished general condition and gastrointestinal side effects of the medications used to treat COVID impair oral intake.

Discussion

Nausea and vomiting are common side effects seen with antiviral and antiinflammatory medications (i.e. antiviral agents, nonselective COX inhibitors, steroids). Taken together with increased vasoconstriction seen in COVID, decreased enteral nutrition leads to intestinal epithelial atrophy. In the treatment of burn patients, maintenance of enteral nutrition is of paramount importance. Burn patients with systemic inflammatory response are universally fed via enteral route (e.g. by nasoduodenal tubes) to ensure hyperalimentation to cope with hypermetabolic state. A similar state is seen in COVID patients and nutritional aspect of supportive treatment is overlooked most of the time.

Conclusion

Burn injury triggered systemic inflammatory response syndrome (SIRS) and COVID share many pathophysiologic features. Mannose binding lectin pathway, NLRP3 and endothelial glycocalyx are three keywords of this review. Chemical inhibition or modification of various targets in the pathophysiology of COVID should be supplemented with a global supportive treatment. Since there are many shared features of burn injury and COVID, main dimensions of burn treatment should be reviewed and investigated in the treatment of COVID.

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