

# Role of Harmful Molecules in the Pathogenesis of Sepsis: A Review

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**Sepsis, a common condition encountered in hospital environments and remains an important cause of death at intensive care units. There are many factors such as genetics, physical agents, mediators and effectors involved in the development of sepsis. A marked increase in serum procalcitonin during the course of a septic process often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement. The patient's immune surveillance could fail to eliminate the pathogen, allowing it to spread and there is a pro-inflammatory mediator release with, inappropriate activation.** *Journal of Nature and Science, 1(8):e142, 2015.*

Sepsis | SIRS | innate immune system | procalcitonin | steroids | reactive oxygen species

## Introduction

Sepsis is the leading cause of mortality especially in non-cardiological critically ill patients with as many as 20 million cases of sepsis annually worldwide and a mortality rate of around 35%. [1]

Doerfler recently reported on methods for reducing sepsis mortality in emergency departments and inpatient units at North Shore-LIJ. The authors stated at their center they had reduced overall sepsis mortality by approximately 50% in a six-year period (2008-2013; sustained through 2014) and increased compliance with sepsis resuscitation bundle elements in the EDs and inpatient units in the 11 acute care hospitals. Improvements were achieved by engaging leadership; fostering inter professional collaboration, collaborating with other leading health care organizations; and developing meaningful, real-time metrics for all levels of staff. [2]

Levy reported on surviving a sepsis campaign (SSC) and an association between performance metrics and outcomes in a 7.5-year study.<sup>3</sup> Compliance with the SSC performance bundles, which were based on the 2004 SSC guidelines and measured in 29,470 subjects entered into the SSC database from January 1, 2005, through June 30, 2012. Compliance was defined as evidence that all bundle elements were achieved. Two hundred eighteen community, academic, and tertiary care hospitals in the United States, South America, and Europe. Patients were selected from the emergency department, medical and surgical wards, and ICU who met diagnosis criteria for severe sepsis and septic shock. [3] This analysis demonstrated that increased compliance with sepsis performance bundles was associated with a 25% relative risk reduction in mortality rate. Every 10% increase in compliance and additional quarter of participation in the SSC initiative was associated with a significant decrease in the odds ratio for hospital mortality. These results demonstrated that performance metrics can drive change in clinical behavior, improve quality of care, and may decrease mortality in patients with severe sepsis and septic shock. [3]

Dysregulation of the hemostatic system due to the interaction between the coagulation system and the inflammatory response is a strong predictor of mortality in patients with severe sepsis.

## Sepsis Definition, SIRS and Complement

Sepsis, defined as infection-induced systemic inflammatory response syndrome (SIRS) involves multiple mechanisms, including the release of cytokines, the activation of complement systems, coagulation systems and fibrinolytic systems. [4]

Frieri reviewed an earlier article that considered some basic aspects of complement biology, addressing the clinical effects of hereditary complement deficiencies and the role of complement

related to host cell entry, pathogenesis of infectious diseases, and apoptosis. [5]

## Role of Cytokines

Bone in an earlier review studied the pathogenesis of the systemic inflammatory response syndrome and what we do and do not know about cytokine regulation and analyzed the roles of cytokines, cytokine production, and the relationship of cytokine production to the development of SIRS. [6] He stated a three-stage development of SIRS was proposed by as stage 1, a local production of cytokines in response to an injury or infection, stage 2, the protective release of a small amount of cytokines into the circulation and stage 3 as the massive systemic reaction where cytokines become destructive by compromising the integrity of the capillary walls. [6]

Cytokines are generally viewed as a destructive development in the patient that generally leads to multiple organ dysfunction. However, cytokines also protect the body when localized and It will be necessary to study the positive effects of cytokines and their role in causing SIRS and to investigate the relationship between cytokines and their blockers in SIRS. [6]

Cytokines have been implicated in the pathogenesis of sepsis. Macrophages phagocytose bacteria and produce a range of proinflammatory cytokines, which initiate the innate immune system's response to the bacterial pathogen. This result in the production of interleukin (IL)-1 $\beta$ , tumor necrosis factor (TNF), and IL-6. The surge of proinflammatory cytokines during the innate immune response is a clinically visible and widely studied aspect of the pathophysiology of sepsis. [7]

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Measurements of thioredoxin (Trx), macrophage migration inhibitory factor (MIF), IL-6, -8, IL -10 and procalcitonin (PCT) in plasma from patients with SIRS/sepsis, neutropenic sepsis, healthy volunteers and pre-oesophagectomy patients were evaluated. [8] Plasma levels of Trx, MIF, IL-6, -8, -10 and PCT were raised in patients with SIRS/sepsis. Comparisons between mediators suggested a unique correlation of Trx with MIF. Trx and MIF differed from cytokines and PCT in that levels were significantly lower in patients with neutropenia compared with the main SIRS/sepsis group. By contrast, IL-8 and PCT levels were significantly greater in the neutropenic patient group. The link between MIF and Trx highlighted in this study has implications for future investigations into the pathogenesis of SIRS/sepsis. [8]

IL-7 has been shown to increase lymphocyte proliferation, expression of lymphocyte adhesion molecules, lymphocyte function-associated antigen 1 and very late antigen-4, interferon- $\gamma$  production, and CD28 expression on splenic CD8+ T cells. [9] Combined treatment with IL-7 and anti-programmed cell death 1 antibody (anti-PD-1) produced additive effects on CD28 expression, lymphocyte proliferation, and splenic secretion of interferon- $\gamma$ . Thus, there are differences in immunomodulatory actions between IL-7 and anti-PD-1, and provides a potential rationale for combining IL-7 and anti-PD-1 in the therapy of sepsis. [9]

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### Role of Procalcitonin

Investigators discovered that the levels of procalcitonin, the precursor of the hormone calcitonin, were elevated in patients with bacterial infection, and it emerged as another potential biomarker. Increased plasma procalcitonin was suggested to be added to the updated definition of sepsis in 2003, as one of the diagnostic criteria for sepsis.[10]

The primary pathophysiological trigger for the increase of serum procalcitonin is infection, whether exogenous in origin or via endogenous translocation of bacterial toxins across the gut wall or other epithelial barriers.[11] Subsequent investigations identified procalcitonin as part of the complex pro-inflammatory response of the innate immune system.[11] Procalcitonin has been considered as a potential therapeutic target because its administration to septic animals exacerbated mortality, which was subsequently alleviated after neutralization of calcitonin precursors.[12] During the course of a septic process, a marked increase in serum procalcitonin often indicates an exacerbation of the illness, and a decreasing level is a sign of improvement.

Procalcitonin circulates at very low concentrations in normal serum and the concentrations of procalcitonin, measured by monoclonal immunoradiometric assay, were found to be elevated during septic conditions. In sepsis, the serum levels of procalcitonin usually increase markedly, attaining values of tens, to hundreds, to thousands-fold that of normal levels.[13]

Procalcitonin was found to be a more accurate diagnostic parameter for sepsis, and therefore daily determinations of procalcitonin may be helpful in the follow up of critically ill patients.[14,15]

Many randomized controlled trials suggest that using clinical algorithms based on procalcitonin levels results in reduced antibiotic. A systemic review of these trials revealed that measurement of procalcitonin levels for antibiotic decisions in patients with sepsis appears to reduce antibiotic exposure without worsening the mortality rate.[16]

Procalcitonin is a recently rediscovered biomarker that fulfills many of these requirements, especially in comparison to other commonly used biomarkers, and that has demonstrated superior diagnostic accuracy for a variety of infections, including sepsis.[17] Procalcitonin algorithms are based on daily measurement of procalcitonin and clinical signs & symptoms of infection. Implementation of a procalcitonin-protocol in a real-life clinical setting was associated with a reduced duration of antibiotic therapy in septic patients without compromising clinical or economical outcomes.[18]

### Vitamin D and Sepsis

Chen determined whether vitamin D levels correlate with procalcitonin levels and mortality in septic patients.[19] Lower serum 25OHD levels at ICU admission were associated with 28-day mortality in septic patients. Serum 25OHD levels were inversely correlated with PCT levels. Hypovitaminosis D was associated with higher mortality rates in PTH responders than in nonresponders.[19]

Frieri reviewed vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms stating deficiency has been implicated in various diseases such as diabetes, high blood pressure, cardiovascular disease which can be associated with sepsis, and many cancers.[20] It has also been implicated in several allergic disorders and immune system dysregulation. There was also a positive correlation with allergy subtypes such as prevalence of rashes, and sinus infections with low vitamin D. VDD related to the immune system dysregulation.[20]

### Role of Steroids in Sepsis

Frieri reviewed corticosteroid effects on cytokines and chemokines and stated cytokines as soluble proteins or growth

factors are involved in cellular interactions are major contributors to allergic and immune-mediated inflammation and chemokines are chemoattractive cytokines subdivided into families based on cysteine residues.[21] This review considered only a selected number of several of these proteins and stated characteristics of several major cytokines up to IL-15, chemokine targets and the effect of corticosteroids on various cells, cytokines, and chemokines. The effect of corticosteroid inhibitors of non-specific endothelial activation, selective activation of VCAM-1 expression, eosinophil priming and chemokine production related to allergic diseases was illustrated.[21]

Marik developed consensus statements for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients and stated methylprednisolone in a dose of 1 mg x kg(-1) x day(-1) for > or = 14 days is recommended in patients with severe early acute respiratory distress syndrome. Glucocorticoids should be weaned and not stopped abruptly. Reinstitution of treatment should be considered with recurrence of signs of sepsis, hypotension, or worsening oxygenation.[22]

Póvoa in a recent study evaluated the clinical impact of the administration of intravenous steroids, alone or in conjunction with drotrecogin-alfa (activated) (DrotAA), on the outcomes in septic shock patients.[23]

A total of 1695 patients were enrolled of which 49.5% received intravenous steroids for treatment of septic shock at baseline (DrotAA + steroids N=436; DrotAA + no steroids N=414; placebo + steroids N=403; placebo + no steroids N=442). In the present study of septic shock patients, after adjustment for treatment selection bias, the authors were unable to find noticeable positive impact from intravenous steroids for treatment of septic shock at baseline either in patients randomized for DrotAA or placebo.[23]

### Reactive Oxygen Species (ROS) and Sepsis

Neutrophils play an essential role in the body's innate immune response to infection. To protect the host, these phagocytic cells possess an impressive array of microbicidal weapons that can be brought to bear on an invading pathogen, including a variety of toxic oxygen radical species and proteolytic enzymes.[24]

Quinones are electron and proton carriers that play a primary role in the aerobic metabolism of virtually every cell in nature. They undergo highly regulated redox reactions in the mitochondria, Golgi apparatus, plasma membrane and endoplasmic reticulum. Important consequences of these electron transfer reactions are the production of and protection against reactive oxygen species (ROS).[25]

A review of the literature revealed an inflammatory response and an increased production of reactive oxidative species (ROS) to be common immune responses to nanomaterial use. The mechanisms by which the inflammatory response and ROS production occur was also discussed.[26]

### Conclusion

This review has covered sepsis and the systemic immune response, the role of cytokines and procalcitonin, role of steroids in sepsis, innate immunity and reactive oxygen species related to sepsis and the impact on neutrophil function. Procalcitonin has been proved to be superior biomarker in terms of diagnosing sepsis and predicting clinical outcome and the use of procalcitonin should be considered within the context of the clinical workup including patient history, physical examination and other laboratory findings. Integrating use of procalcitonin into practice in the early golden hours of sepsis diagnosis and antibiotic stewardship program would be beneficial. There is still a need for better understanding of how procalcitonin fits in the immune response, and further studies and efforts should be towards exploring the immunological role of procalcitonin in sepsis.

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