Chapter 5
Sepsis-Induced Immune Suppression

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Introduction

Newton's third law is commonly quoted as "for every action, there is an equal and opposite reaction." This concept was largely ignored in the initial theories regarding the body's response to overwhelming infection, which was characterized as a surge of inflammation that arises to eliminate invading pathogens, and may injure the host organism along with it. This leads to the concept that it may be possible to ameliorate the organ damage in sepsis by reining in this unmitigated inflammatory response. Indeed, many early preclinical studies showed some initial promise in mitigating sepsis mortality in animals by limiting the pro-inflammatory response. However, a large number of clinical trials in humans of a variety of anti-inflammatory therapies failed to demonstrate any improvement in the high mortality associated with sepsis [1].

In 1996, Roger Bone invoked Isaac Newton in a landmark editorial discussing possible explanations for the failure of anti-inflammatory therapies in sepsis [2]. Bone and others recognized that there was a growing body of evidence demonstrating immunosuppression following other forms of inflammation such as surgery or trauma. He reviewed the existing evidence showing that the immune response to sepsis is not nearly as straightforward as was originally held. In addition to the pro-inflammatory response to sepsis, there is a concomitant anti-inflammatory response. He postulated that the balance between these two intertwined responses largely

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determines the outcome in sepsis and coined the term "Compensatory Anti-inflammatory Response Syndrome" (CARS) to describe the anti-inflammatory response.

Thus was created a more nuanced view of sepsis as a pathologic dysregulation of the immune system with both pro- and anti-inflammatory effects. Bone hypothesized that overwhelming infection disrupts the body's normal homeostasis such that at different points within the time course of infection pro-inflammatory or anti-inflammatory forces may predominate, either of which can be pathologic and contribute to mortality. The most straightforward theory resulting from these ideas holds that the early course of sepsis is characterized by the traditional pro-inflammatory response, with capillary leak, organ dysfunction, and (if left unchecked) death. This is then followed by a period of immune suppression during which the body is susceptible to secondary infections (and subsequent death) before returning to homeostasis. The relative strength of the pro- and anti-inflammatory responses likely depends on the host and the pathogen, as well as on external interventions (i.e., medical care), resulting in multiple potential immunologic responses.

Two terms critical to the discussion of this topic are immunosuppression and immunoparalysis. For the purposes of this chapter, immunosuppression should be considered to be the active anti-inflammatory responses (such as increased secretion of anti-inflammatory cytokines, and increases in immune suppressor cell populations). Immunoparalysis should be considered the loss of any discernible function that occurs in some cell populations in this process, i.e., anergy. There is now overwhelming evidence demonstrating the clinical importance of sepsis-induced immune suppression along with the general idea of an initial pro-inflammatory state giving way to a later anti-inflammatory state. Almost 2/3 of deaths due to sepsis occur after hospital day 5, during a phase marked by an increase in the percentage of positive cultures due to normally nonpathogenic organisms [3]. Critically ill patients have also been shown to have high rates of reactivation of dormant viruses such as cytomegalovirus (CMV) and herpes simplex virus (HSV) [4, 5]. This chapter will review the current understanding of sepsis-induced immune suppression.

Cytokines in Sepsis-Induced Immune Suppression

Cytokines play a significant role in mediating the immune response of the body. While specific pathways of activation of individual cytokines are nuanced, many can be generally labeled as either pro-inflammatory or anti-inflammatory. Some well characterized pro-inflammatory cytokines include interleukin 1 (IL-1), IL-6, IL-12, tumor necrosis factor α (TNFα), and interferon γ (IFNγ). Anti-inflammatory cytokines include IL-4, IL-10, and transforming growth factor β (TGFβ) although these cytokines can have proinflammatory effects in other conditions [6, 7]. Both pro- and anti-inflammatory cytokine production is stimulated early on in response to infection.

An illustrative study demonstrating this was done by Novotny et al. [8]. Measurements of IL-6 and IL-10 were taken from human patients with postoperative sepsis as well as in a murine model of septic peritonitis. The initial immune response in both study populations was characterized by concomitant increases in IL-6 and IL-10. Further, the relationship was exponential such that a linear increase in the pro-inflammatory cytokine IL-6 correlated with an exponential increase in the anti-inflammatory cytokine IL-10. This suggests that the body engages in an immediate attempt to rein in the pro-inflammatory response that is unleashed in response to infection.

IL-10 is currently thought to be the most important of the anti-inflammatory cytokines [6]. It was first characterized around 1990 when it was shown to regulate T-cell populations [9, 10]. It has now been established that IL-10 has multiple immunosuppressive roles, with most important being the downregulation of TNF [11]. In animal models of sepsis, the administration of IL-10 has been shown to have both positive [12–14] and negative [15, 16] effects on outcome, which likely depend on the time of administration and the severity of the infection. In one carefully done animal model, Ashare and colleagues [17] followed levels of pro-inflammatory and anti-inflammatory cytokines throughout the whole course of sepsis in mice. They found that bacterial levels in tissue correlated with IL-10 levels and that if the pro-inflammatory response was blocked by pretreatment with IL-1 receptor antagonist, bacterial levels were higher, as was mortality. Similarly, Song and colleagues [18] showed that blocking IL-10 activity early had no effect on mortality, whereas blocking it late (12 h) after sepsis improved mortality. This suggests that in the pro-inflammatory milieu of early sepsis, IL-10 does not have a major role, whereas in the later phase of disease when immunosuppression predominates, its effect is more pronounced.

The Role of Immune Cells in Sepsis-Induced Immunosuppression

Impaired Immune Cell Function and Programmed Cell Death in Sepsis

Activated by triggers such as antigens or inflammatory cytokines, immune cells speed the death and clearance of infectious organisms in sepsis. This immune protection comes at a cost however, as immune cell activity can lead to tissue and organ injury through the release of anti-infective products such as oxidants. As the sepsis inflammatory cascade develops, the body begins the process of inhibiting these immune cells through two processes, deactivation of immune cell function and apoptosis.

Some of the earliest studies in impaired immunity in states of inflammation noted impaired immune cell function manifest as anergy [19]. Later studies were able to characterize an array of immune cell dysfunction that accompanies severe inflammation (reviewed below). Cell death is a common process and can occur via two pathways, apoptosis or necrosis. Apoptosis, or programmed cell death, is a carefully regulated process by which the body can allow for cell turnover without inducing inflammation (as occurs with necrosis) [20]. Apoptosis of immune effector cells is an important mechanism by which the body regulates the intensity and duration of a pro-inflammatory state. Many animal and human studies in sepsis have shown extensive apoptosis of immune effector cells including B and CD4+ T lymphocytes, dendritic cells, and epithelial cells [21–24]. Additionally, the subsequent burden that clearing these apoptic cells plays on the remaining immune cells is thought to be a major contributor to immunoparalysis.

Neutrophils

Neutrophils play a critical role in the body's response to infection, so it is not surprising that they are intricately involved in the balance between pro- and anti-inflammatory pathways in sepsis [25]. In contrast to many other immune cells, the apoptosis of neutrophils is down-regulated in sepsis [26, 27]. This was shown by Tamayo et al. in a prospective observational study of 80 septic patients and 25 healthy controls [27]. The rates of neutrophil apoptosis were decreased at 24 h, 5 days, and 12 days after diagnosis of sepsis in comparison to controls. There was no difference seen between survivors and non-survivors of sepsis.

Additionally, immature neutrophils are released in a large number from the bone marrow, resulting in the neutrophilia with bandemia seen in many patients presenting with sepsis [28]. These immature neutrophils are immunologically active. This was shown in a prospective observational study by Drifte et al. [28]. Whole blood from 33 ICU patients with sepsis, 12 ICU patients with SIRS, and 32 healthy volunteers was taken and immune function was assessed in vitro. Immature neutrophils were able to engage in phagocytosis and bacterial killing via production of reactive oxygen species, although less efficiently than mature neutrophils. Interestingly, immature neutrophils exhibited a more pro-inflammatory state, as evidenced by an elevated TNF-alpha/IL-10 ratio. This is important as mature neutrophils have been shown to be involved in the anti-inflammatory response of sepsis via the production of IL-10 [29]. This balance between a pro-inflammatory and anti-inflammatory state in neutrophils has been shown to predict the development of secondary infections that are so often the actual cause of mortality in sepsis. Stephan et al. studied in vitro neutrophil function in patients with sepsis 4 days after they had been admitted [30]. They found that those patients who subsequently developed a nosocomial infection exhibited impaired phagocytosis and bacteriocidal killing at day 4.

Antigen Presenting Cells

Dendritic Cells

Antigen presenting phagocytes, including dendritic cells and macrophages, play a critical role in the immune response to infection [20, 31, 32]. Tinsley et al. investigated dendritic cell populations in a murine model of sepsis [24]. They found a rapid proliferation in follicular dendritic cells in the first 36 h after infection that was followed by extensive apoptosis, resulting in a net decrease in dendritic cell numbers by 48 h. Fujita et al. identified a subset of regulatory dendritic cells that activate anti-inflammatory pathways via the secretion of IL-10 [32]. Additional studies have also identified a shift in phenotype of dendritic cells toward an anti-inflammatory pathway in patients with sepsis-induced immunosuppression [33, 34]. These findings are in keeping with the model of sepsis as a balance between pro- and anti-inflammatory immune responses.

Multiple studies have examined the importance of dendritic cells to the immune response to sepsis. In a straightforward study, Guisset et al. measured peripheral blood dendritic cell counts in patients with sepsis [35]. They found that an early decrease in dendritic cell numbers correlated strongly with subsequent mortality and hypothesized that this may be a useful prognostic biomarker in septic patients. Toliver-Kinsky et al. have extensively studied the ability of a dendritic cell growth factor, FLT3 ligand, to impact murine resistance to pseudomonal infection in burns. They have shown that FLT3 ligand improves murine resistance to infection via improved neutrophil function in a dendritic-cell-dependent manner [36, 37].

Monocytes/Macrophages

In contrast to dendritic cells, macrophage populations are not reduced in response to sepsis [31]. However, numerous studies have demonstrated that monocytes/macrophages effectively undergo “cellular reprogramming" with a transition from a pro-inflammatory, immune activating response to an immunosuppressing anti-inflammatory response [38, 39]. Indeed, the impaired monocyte response to lipopolysaccharide (LPS), the immunogenic cell membrane component of gram-negative bacteria, seen in sepsis, labeled “endotoxin tolerance,” is considered to be a hallmark of the disorder. These alterations in monocyte function were shown in a study by Munoz et al. using plasma from patients in the ICU with sepsis or non-septic shock [40]. Monocytes isolated from patients with sepsis exhibited impaired release of IL-1, IL-6, and TNF-alpha in response to LPS exposure. Further, sepsis survivors recovered their capacity to respond to LPS exposure whereas non-survivors did not. Monneret et al., while investigating the anti-inflammatory response in sepsis, showed a down-regulation of HLA-receptor expression on monocytes which correlated strongly with levels of the anti-inflammatory cytokine IL-10 [41].

Lymphocytes

Natural Killer Cells

Lymphopenia is a frequent finding in sepsis with reductions in all lymphocyte subtypes [42]. In addition to a reduction in cell number, there is also evidence for cellular reprogramming similar to that seen in antigen presenting cells. Natural Killer (NK) cells are part of the innate immune response and were originally described based on their ability to kill leukemic cells [43]. They play an important role in the early response to infection, largely through production of IFNγ. Similarly to other lymphocyte populations, a reduction in NK cell numbers has been demonstrated in septic patients [42, 44]. A higher percentage of NK cells correlates with improved survival in septic patients [45]. Sepsis may result in NK cell tolerance to antigen stimulation, resulting in impaired production of IFNγ [44, 46, 47].

Chiche et al. demonstrated the clinical importance of this in a study of CMV reactivation in septic patients in the ICU [48]. Patients with sepsis admitted to the ICU were followed prospectively with serial monitoring of NK cell function while assessing for CMV reactivation. At baseline there was no difference in NK cell effector function between cases and controls. However, prior to CMV reactivation, there was a decrease in the ability of NK cells to secrete IFN-gamma (and elevations in serum IL-10 and IL-15 levels).

CD4+ T_H Cells

CD4+ helper T cells are typically divided into two distinct subtypes, Th1 and Th2, based on their pattern of cytokine secretion in response to stimulation. Th1 cells release pro-inflammatory cytokines including TNF-a, IFN-g, and IL-2, whereas Th2 cells release anti-inflammatory cytokines including IL-4 and IL-10 [6]. Sepsis has been shown in some studies to result in a shift toward a pro-Th2 response with the release of more anti-inflammatory cytokines, whereas other studies have shown an overall suppression of both Th1 and Th2 cells [6, 39]. These findings are consistent with the development of both immune suppression and immunoparalysis.

A third population of helper T cells, Th17 cells, has also been identified as playing an important role in sepsis-induced immune suppression. These cells are important in protecting against extracellular bacterial and fungal infections via secretion of IL-17 and IL-22. Th17 cells are also decreased in septic patients and loss of effective Th17 function is thought to contribute to the occurrence of secondary fungal infections in sepsis-induced immune suppression [39, 42, 49].

γδ T Cells

γδ T cells are present in high numbers in the intestinal mucosa and can be considered first line defenders against particular pathogens. In 2005, Venet et al. showed that γδ T cells decrease in patients with sepsis [50]. In the largest study to date, Andreu-Ballester et al. studied 135 patients with sepsis from an emergency department and intensive care unit. All the γδ T cell populations decreased significantly as the septic picture worsened. Almost 20% of patients died and the γδ T cells were significantly reduced in those septic patients who died. In this study, γδ T cells showed the largest decrease of any T cell population and the reduction correlated with sepsis severity [51].

Regulatory T Cells

Regulatory T cells (T_{Reg}), formerly known as suppressor T cells, are a subpopulation of CD4+ T cells that play an important role in modulating the immune response [39]. T_{Reg} levels are elevated in patients with sepsis compared to controls, and higher levels (along with more immunoparalysis) are seen in non-survivors compared to survivors [52, 53]. Several studies have attempted to elucidate the mechanisms by which T_{Reg} cells may directly contribute to immunoparalysis. T_{Reg} cells have been shown to redirect monocytes and macrophages into an anti-inflammatory alternative activating macrophages (AAM) pathway. This was partly through T_{Reg} production of IL-10, but also through a cytokine-independent pathway [54]. T_{Reg} cells also inhibit the memory γδ T cell production of IFN-γ in response to antigen challenge [55].

Predicting Clinical Outcomes with Biomarkers of Sepsis-Induced Immunosuppression

There have been many efforts to study the timing and magnitude of the immunosuppressive response in relation to patient outcomes which would create effective biomarkers for prognosis and therapies [56]. In 1983, Keane et al. studied lymphocytes cultured from 31 patients with severe trauma. They found that, overall, lymphocyte response to stimulation with mitogens was markedly reduced from controls. Furthermore, responses were lower and the duration of suppression longer in those patients who became infected, and the suppression of response preceded the onset of infection. Extremely low responses were found in three patients who later died [19].

More commonly, studies of patient's monocytes and their own HLA receptor down regulation have shown promise as a biomarker [57–66]. Asadulla et al. studied 57 neurosurgical patients and found that HLA-DR expression was lower in 14 patients who developed infection, compared with patients with an uncomplicated

postoperative course [57]. Out of ten patients with less than 30% HLA-DR positive monocytes, nine developed infection. They hypothesized that the mechanism of this down regulation was high levels of endogenous cortisol as the effect coincided with high ACTH and cortisol concentrations and similar down regulation was seen in other patients who received high doses of exogenous corticosteroids. Subsequent studies supported the theory that the magnitude of HLA-DR receptor down regulation predicted a variety of other poor outcomes such as sepsis in liver transplant patients [58], however that study was confounded by exogenous steroids in some patients [60]. Allen et al. found HLA levels predicted sepsis in pediatric cardiac surgery patients [67]. In a small study of septic adults, Su et al. found that levels of HLA-DR positive monocytes <30% were more predictive of mortality than APACHE II scores [65].

The predictive power of monocyte deactivation has not been shown consistently, however and more recent studies have yielded different results. In 2003, three papers were published that seemed to contradict earlier findings. Hynninen et al. evaluated the HLA-DR expression of 61 patients with sepsis at admission and showed no predictive power of HLA expression for survival [61]. Another study of 70 septic patients also found no correlation between HLA expression and infectious or mortality outcomes [63]. Interestingly, this study showed that if patients' monocytes were stimulated with G-CSF ex-vivo, their HLA expression increased. The third study looked at 85 cardiac surgery patients. HLA expression was measured at presurgery, immediately after and 1 day later. Their data showed that while all patients' HLA levels declined after surgery, the magnitude of the response did not correlate with sepsis/SIRS, or other infectious complications [62]. Reasons for the different results are unclear but may be the result of small sample sizes, timing, or well-described variation caused by the different laboratory techniques used. In one study, the same samples were analyzed in two different labs and differed by as much as 20% [62].

Other studies have looked at anti-inflammatory cytokine levels as predictors of poor outcomes; most of these studies have been on human patients and bore mixed results. These data likely reflect the varied magnitudes and time courses of both pro and anti-inflammatory cytokine expression in real patients. In 1998, Doughty et al. sampled 53 pediatric ICU patients and found that high IL-10 levels correlated with three or more organ dysfunction and mortality [68]. Ahlstrom found no predictive value in IL-10 levels in patients with SIRS [64] but Simmons et al. found that IL-10 levels did correlate with mortality in a sample of 93 critically ill patients with acute renal failure [69]. Perhaps the most interesting data comes from two studies that looked at the ratio of IL-10 to TNF. In a large study of over 400 patients admitted to the hospital for fever, van Dissel et al. showed that a higher IL-10 to TNF ratio was predictive of mortality [70]. A similar study by Gogos et al. in a population of patients with mixed sepsis showed the same results [56].

A postmortem study by Boomer et al. compared patients who died in the intensive care unit (ICU) from severe sepsis with control patients who died of other causes. They found evidence of both immunosuppression and immunoparalysis in patients who died of sepsis. There was a marked change in the balance between suppressor

cell populations and immunogenic cell lines including splenic CD4, CD8, and HLA-DR cells. Additionally, they found that patients who died of sepsis had <10% of the levels of both pro-inflammatory cytokines (TNF-α, IFN-γ, IL-6) and anti-inflammatory (IL-10) cytokines compared to patients dying of other causes [71].

Potential Therapeutic Interventions in Sepsis-Induced Immune Suppression

Decades of research in sepsis-induced immunosuppression has fostered the concept that both the pro and anti-inflammatory responses are necessary for recovery from an overwhelming infection and that it is the imbalance of these forces that can lead to organ injury and death. This has led some investigators to explore manipulation of these systems to improve outcomes. While some animal studies in this field have shown positive results, many have not and it is clear that in a system as complicated as sepsis the timing and dose of any agent used to affect the degree of pro or anti-inflammatory response are crucial factors.

Some of the first agents used to manipulate the balance of immunosuppression were androgens and estrogens. The idea for hormonal therapy came from earlier studies showing that testosterone seemed to have a negative impact on sepsis and trauma outcomes and is believed to act through augmenting postinjury immunosuppression [72]. Two subsequent studies by the same investigators showed that administration of the estrogen-like drug DHEA reduced the immunosuppression and improved mortality in septic mice [73, 74]. By far, most of the studies that have tried to manipulate the balance of inflammation have involved using anti-inflammatory cytokines that are here reviewed.

Interleukin-10

In animal models of sepsis, the administration of IL10 has been shown to have both positive [12–14] and negative [15, 16] effects on outcome which likely are dependent on the time of administration and the severity of the infection. In one carefully done animal model, Ashare et al. followed levels of pro-inflammatory cytokines and anti-inflammatory cytokines throughout the whole course of sepsis in mice. They found that bacterial levels in tissue correlated with IL-10 levels and that if the complementary pro-inflammatory response was blocked by pretreatment with IL-1 receptor antagonist, bacterial levels were higher as was mortality [17]. Similarly, Song et al. showed that blocking IL-10 activity early had no effect on mortality, blocking it late (12 h) after sepsis improved mortality [18]. These studies help illustrate how IL10 helps maintain a careful balance of the immune system in inflammation; thus, manipulation of it is so dangerous.

Interleukin 7 (IL-7)

Interleukin 7 may be the immunomodulatory agent that is closest to clinical utility in sepsis as it has shown positive results in animal trials of sepsis as well as has been shown to be safe in clinical trials in humans for other disease processes. IL-7 plays a critical role in T cell function. Mutations in IL-7 are one of the causes of severe combined immunodeficiency (SCID) [75–77]. In a murine model of sepsis, IL-7 has been shown to prevent loss of T-cells by both decreasing T-cell apoptosis and increasing T-cell proliferation. This prevented the loss of delayed type hypersensitivity (DTH) response and improved overall survival [78, 79]. A phase I/IIA study in humans with HIV and persistent lymphopenia despite combination anti-retroviral therapy demonstrated sustained increases in CD4 and CD8 T cells without signs of a hyper-inflammatory response or other adverse effects [80].

Interleukin 15 (IL-15)

IL-15 is closely related to IL-7 [78]. It is an anti-apoptotic cytokine that is regarded as a promising immunomodulatory therapy in cancer [81]. In murine models of sepsis, it has been shown to block apoptosis through the BCL-2 pathway, resulting in improved IFNγ production and reversal of sepsis-induced immunosuppression, which leads to improved survival [82]. Technical challenges related to rapid renal clearance of its recombinant form have limited its efficacy in human studies to date, but further trials are ongoing [81].

Programmed Cell Death Receptor-1 (PD-1) and Programmed Cell Death Ligand-1 (PD-L1)

PD-1 and PD-L1 are part of a family of co-inhibitory cell surface molecules that have been studied as another promising immunomodulatory therapy. PD-1 is expressed by activated T-cells and PD-L1 by epithelial, endothelial, and antigen presenting cells. PD-1/PD-L1 binding is thought to be part of the negative feedback loop that is triggered by an activation of the immune system. In the presence of prolonged antigen presence, this may lead to T cell exhaustion. Blocking the PD-1/PD-L1 pathway has shown extreme promise in cancer immunotherapy in human trials [83, 84]. In studies of human septic patients, PD-1 and PD-L1 expression has been shown to be upregulated in T cells and monocytes respectively [85, 86]. Further, levels of expression of PD-1 and PD-L1 correlated with increased secondary infections and mortality [86]. In murine models of bacterial sepsis as well as in both primary and secondary fungal sepsis, blockade of this pathway has resulted in improved survival [87, 88]. Human studies of anti-PD-1 and anti-PD-L1 have not yet been performed.

Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)

Loss of immune cells is an important factor in sepsis-induced immune suppression. Stimulating immune cell production has been looked at as a therapeutic target. Initial studies focused on granulocyte stimulating factor (G-CSF), which resulted in a marked increase in neutrophil number, but no change in clinical outcomes [89, 90]. Given the loss of cell types other than neutrophil as well as the importance of non-neutrophil immune cells in fighting the secondary viral and fungal infections that are common in sepsis-induced immune suppression, subsequent studies have focused on inducing a broader immune response with GM-CSF. Two such studies in humans have shown promising results, and are also notable for their use of a biomarker-based approach for identifying patients in the immunosuppressed phase of sepsis [91, 92]. While neither study was powered to show a difference in mortality, both showed improvement in markers of immune function (specifically TNF-α production) in patients treated with GM-CSF.

Interferon-Gamma

IFNγ is a key downstream mediator activating the innate immune response. IFNγ levels are decreased in patients with sepsis-induced immune suppression. Administration of IFNγ in uncontrolled studies has been shown to restore immune function [93, 94]. At least five studies have examined the use of gamma interferon which has been shown in-vivo to reverse monocyte deactivation [95, 96]. Two very similar small trials were done on human subjects with sepsis [93, 97]. In both studies, subjects with sepsis and monocyte HLA-DR expression of 30% or less were given interferon gamma. Both groups reported increases in HLA-DR expression, usually after just one dose. One of the studies also examined the monocytes ex-vivo and showed that interferon improved monocyte cytokine production as well [93]. A third human trial was different in that it sought to study the effects of Interferon gamma regionally [98]. In this study, the authors selected 21 patients with severe trauma and alveolar macrophage dysfunction as determined by a bronchoalveolar lavage sample showing macrophage HLA-DR expression of 30% or less. Interferon gamma was administered via inhalation. They found about 50% of the subjects had an increase in their alveolar macrophage HLA-DR expression. These patients had a lower incidence of pneumonia but no other differences in outcomes. The small numbers and lack of a control population in all three of these studies limit the conclusions that can be drawn, especially since HLA-DR expression is known to increase as patients recover. A small randomized controlled trial of IFNγ in sepsis is ongoing (ClinicalTrials.gov number: NCT01649921).

Conclusion

Sepsis-induced immune suppression is likely a major contributor to the morbidity and mortality associated with sepsis. It is characterized by a decrease in immune effector cell number as well as loss of function, which results in increased susceptibility to secondary infections. Potential therapies to augment the immune response show promise as a means to decrease sepsis-related mortality but large randomized controlled trials have not yet been done.

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