Journal of Advanced Biomedical and Pharmaceutical Sciences

JABPS

Journal
Of Advanced Biomedical
And Pharmaceutical Sciences

Cytokines in Sepsis: Friend or Enemy

Shaymaa R. Senousy*, Al-Shaimaa F. Ahmed[iD], Mahmoud El-Daly[iD], Mohamed M. A. Khalifa

Department of Pharmacology and Toxicology, Faculty of Pharmacy, Minia University, Minia, Egypt.

Abstract

Infectious diseases are a major cause of death worldwide. A serious complication of infections is septic shock. Septic shock is a critical syndrome associated with the host response to infection. The severity of infections is related to an activation cascade that results in a magnification of the cytokine production which is termed "cytokine storm". Despite the commonly elucidated etiology of sepsis and its clinical course, the actual progress in therapeutic strategies is still limited. Several studies were carried out on the pathophysiology of sepsis-induced imbalance in the inflammatory/anti-inflammatory response as the main cause of tissue damage, organ failure, and eventually, death. Cytokines are crucial pleiotropic regulators of the immune response, which have an important role in the complicated pathophysiology of sepsis. They possess both pro-and anti-inflammatory properties and are capable of exerting efficacious defense responses towards invading pathogens. On the other hand, cytokines may disturb the immune response and reinforce inflammation. Thus, achieving a balance between these two effects will improve the prognosis of sepsis. Blocking the activities of pro-inflammatory cytokines promotes survival in animal models of sepsis, yet, such a treatment strategy did not enhance the clinical outcome. In this review, we will describe the mechanisms underlying the pathogenesis of the cytokine storm during sepsis and represent in detail the role of cytokines responsible for cell or organ damage. We will compare the various therapeutic approaches investigated to stop or suppress this mischievous process and discuss the reasons for therapeutic failure.

1. Introduction

Sepsis is one of the critical global health issues especially in low- to middle-income countries [1]. The consequences of sepsis are especially undesirable in critically ill patients, immunocompromised, and in the elderly [2]. Studies indicated that the incidence of sepsis is surprisingly high beyond that of myocardial infarction [3] or the combination of breast, lung, and prostate cancer [4].

The etiology of the sepsis remains unclear, despite extensive research. The early understanding was that the main source of infection is only the gut microbiota [5]. Later studies indicated that the most commonly associated infection in sepsis was that of the upper respiratory tract caused by colonization of *Pseudomonas sp.* [6]. Moreover, bacteria are not the only causative agents of sepsis, but also parasitic and fungal infections are involved [7-9]. Although the presence of inflammation was remarkable and remained constant until the 2000s, targeting the inflammatory phase of sepsis appeared to have no remarkable potential in patient survival [10]. Recently, researchers started to believe that inflammation is indeed pivotal to combat pathogens causing sepsis [11]. The implementation of such findings and clinical data into genuine therapeutics remains sophisticated and requires an incorporated view of the synchronization of the cytokine storm and its impacts.

2. Sepsis pathophysiology

Exaggerated primary host response associated with sepsis results in an imbalance between proinflammatory and anti-inflammatory cytokines [12]. The innate immune response responds immediately to invading pathogens [13]. The main regulators of the innate response are the macrophages / monocytes, basophils, neutrophils, eosinophils, and natural killers [NKs]. A wide variety of molecules originating from the infecting microorganism or necrotic cells activate the innate immunity such as the pathogen-associated molecular patterns [PAMPs] and the damage-associated molecular patterns [DAMPs]. These molecules bind to the pattern recognition receptors [PRRs] [14-16] such as the Toll-like receptors [TLRs], the Nod-like receptors, the retinoic acid-inducible gene- receptors, and the C-type lectin receptors [17, 18].

Lipopolysaccharide [LPS], a cell wall component of gram-negative bacteria, was found to act on the TLR4 and is commonly used to study host response following endotoxemia [19]. TLR expression at the cell membrane has a tight control on the regulation of TLR signaling. Higher levels of TLR2 receptors and TLR4 mRNA are detected in septic patients [20, 21].

According to the triggered PRR receptor, certain signaling pathways are activated leading to the upregulation of transcription factors such as Nuclear factor-kappa B [NF-κB] and induction of inflammatory cytokines such as TNF-α, IL-1β, adaptor-protein 1, interferon regulatory factor 3, or IRF7 [22-25]. Production of such molecules results in excessive inflammation and a life-threatening 'cytokine storm' [Figure 1].

The term "cytokine storm" refers to the consecutive release of specific cytokines [26]. Sepsis was believed to be associated with an exaggerated release of only proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-12, macrophage migration inhibitory factor [MIF] and IFN-γ [27]. Although cytokines are responsible for a variety of inflammatory responses, including the migration of immune cells to the site of infection that restrains a localized

---
* *Correspondence: Shaymaa Ramzy Senousy*
Tel.: 01153651918; Fax: +2086-236-90-75.
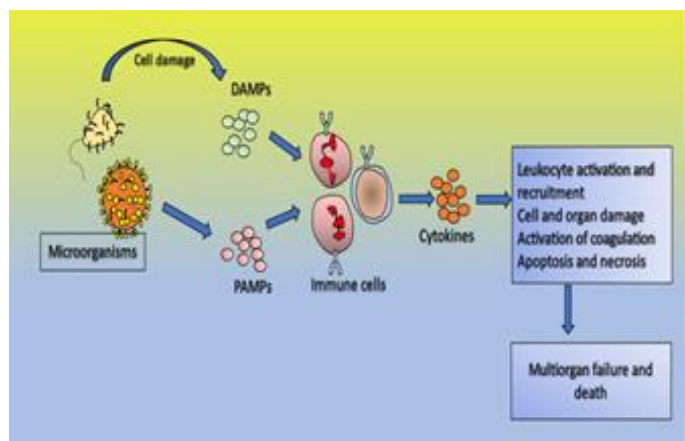*Email Address: Shaymaa.ramzy@yahoo.com*

Figure.1: The cytokine storm starts following activation of PRRs by microbial products (PAMPs or DAMPs) leading by activation of immune cells with subsequent release of inflammatory cytokines which lead to multiorgan dysfunction.

PAMPs: Pathogen Associated Molecular Patterns. DAMPs: Damage Associated Molecular Patterns.
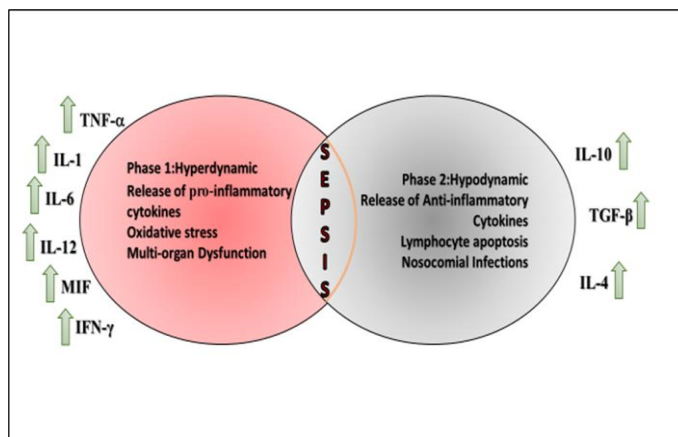

Figure 2: A diagram showing the hyperdynamic and hypodynamic phases evoked during sepsis and the released cytokines during these phases.

TNF-α; Tumor Necrosis Factor- alpha, IL-1β; Interleukin-1 Beta, IL-6; Interleukin-6, IL-12; Interleukin -12, MIF; Macrophage Migration Inhibitory Growth Factor, IFN-Γ; Interferon-Gamma, IL-10; Interleukin-10, TGF-B; Transforming Growth Factor-beta, IL-4; Interleukin-4.

Table 1: most common pro- and anti-inflammatory cytokines released during sepsis

Cytokine	Source cells	Role in sepsis
TNF-α	Monocytes/macrophages**.** T and B lymphocytes, natural killer cells, mast cells, fibroblasts, neutrophils and osteoclasts [in smaller quantities] [37]	Induction downstream inflammatory pathways Induction of thrombotic and fibrinolytic pathways Release of potent vasodilators [38-41]
IL-1β	Blood monocytes, tissue macrophages and dendritic cells [42]	stimulates a cascade of inflammatory mediators [43] Recruitment of leukocytes to the site, activation of endothelial cells, provoking of fever and other systemic symptoms [44]
IL-6	Macrophages, lymphocytes, endothelial cells, dendritic cells, fibroblasts, and smooth muscle cells [45]	Increased migration of activated T cells Induces the production of C-reactive protein [46]
IL-12	Monocytes/macrophages and neutrophils] and dendritic cells [47-49]	Activates NK, CD4+, and CD8+ T cells and induce TH1 differentiation and IFN-γ production [50]
MIF	from DCs, macrophages, monocytes, neutrophils, eosinophils, basophils, lymphocytes, mast cells [51, 52]	Controls the production of IL-6 through regulation of NF-κB [53] Enhances the recognition of LPS by TLR4 so exacerbates of the symptoms of endotoxemia [54, 55]
IFN-γ	NK cells and T lymphocytes [56, 57]	production of several proinflammatory cytokines, chemokines and induction of iNOS following exposure to LPS [58, 59]
IL-10	Activated Th2 subset of CD4+ T cells, monocytes/macrophages, epithelial cell, dendritic cells, keratinocytes, and bronchial epithelial cells [60]	Inhibition of proinflammatory cytokines production [61-63] Inhibits NK cell function [64] and weakens the neutrophil oxidative burst [65]
TGF-β	By many cell types, including macrophages [66, 67]	Decreases the proliferation and differentiation of T cells and B cells Reduces of the percentage of CD4$^+$CD25$^+$Foxp3$^+$ regulatory T-cells [68]
IL-4	T cells, mast cells, and basophils [69-72]	Inhibit the release of inflammatory cytokines [73]. Downregulates the human alveolar macrophages and peripheral blood monocytes [74] Inhibits macrophage activity by blocking their cytotoxic activity and nitric oxide production [75, 76]

infection from being systemic, uncontrolled cytokine release leads to endothelial dysfunction, recognized by vasodilation and increased capillary permeability, hypotension, hemoconcentration, macromolecular extravasation, and edema, which are frequent findings in septic patients and correlate to the resulting leakage syndrome [28]. The dysfunctional epithelial barriers allow pathogens and their products to further infest the host organism, hinder regulatory mechanisms, and cause distant organ dysfunctions [29]. Additionally, growing evidence has indicated that immune and inflammatory responses are tightly intermingled with different physiologic processes within the human host such as metabolism [30, 31] neuroendocrine activation [32, 33], and coagulation pathways [34]. However, certain anti-inflammatory cytokines are pivotal for restraining extreme further inflammation induced-tissue damage trying to retrieve immunological equilibrium. These include IL-10, transforming growth factor [TGF]-β, IL-4, and soluble inhibitors of proinflammatory cytokines, such as soluble TNF receptors [sTNFRs], IL-1 receptor antagonist [IL-1Ra], and soluble IL-1 receptor type II [IL-1R2] [12, 35, 36] [Figure 2 and Table 1]

A highly inflammatory form of programmed cell death; pyroptosis results from the activation of innate response activator B cells which results in IL-3 production and subsequent myelopoiesis in addition to cytosolic inflammasomes, which induce the generation of IL-1β and IL-18 [77, 78]. When those responses are caused by sepsis, these mechanisms can become unregulated and cause a life-threatening inflammatory cascade. This case is different under physiological conditions when these processes allow the innate immune system to eliminate pathogens and damaged cells.

3.Proinflammatory Cytokines

Tumor Necrosis Factor-alpha

Tumor necrosis factor-α [TNF-α] was first identified in 1975. It was found to induce cell death in tumor cells and to have inflammatory effects [79]. It was then regarded as a pivotal target in the management of various inflammatory diseases such as Crohn's disease [80], rheumatoid arthritis [81] and ankylosing spondylitis [82]. TNF-α have been implicated in a large number of infectious diseases as well as in the pathophysiology of sepsis [83]. TNF- α binds to two transmembrane receptors; TNF receptor 1 [TNFR1], and TNF receptor 2 [TNFR2], also known as p55 or p60 and p75 or p80, respectively [84]. Soluble cytokine receptors termed sTNFRs modify the actions of this cytokine and were also found to be correlated with the severity of the disease and mortality in septic patients [85]. Lipopolysaccharide and peptidoglycan- bacterial products- are potent stimulators of TNF release in the pathogenesis of sepsis [86, 87].

Upon investigating different TNF inhibitors [e.g., anti-TNF immune serum, anti-TNF antibodies, sTNFRs, TNFR fusion proteins, TNF siRNA [small interfering RNA], the survival increased in different septic models [e.g., LPS, bacterial, fungal, cecal ligation and puncture [CLP] and pneumonia] [88-90]. But, blocking TNF resulted in worsened microbial clearance and outcome in multiple animal models of infections [91, 92]. Also, an important role of TNF for the host defense was supported in TNF knockout models [93]. Such conflict can be explained by the beneficial role of TNF for host defense during sepsis.

Interleukin-1

Interleukin-1 was recognized as "human leukocytic pyrogen" in 1977 [94]. IL-1 family is a pivotal mediator of immune response to sepsis including two agonists IL-1α and IL-1β both bind to the same cell surface receptor [IL-1RI] and one antagonist [IL-1 receptor antagonist: IL-1ra] [43, 95, 96]. Blocking IL‑1 showed great efficacy in a broad spectrum of inflammatory diseases [97]. Development of shock, multi-organ system failure, and death in septic patients are directly linked to excessive IL-1 production [43].

Unlike the IL-1α precursor which is active and constitutively present in the cells of healthy individuals [42], the IL-1β precursor becomes activated after cleavage by caspase-1 which has to be previously activated by inflammasome [98]. IL-1β participates in the cytokine storm and the production of IL-6 [99]. High levels of IL-1β and TNF-α released from macrophages in sepsis and septic shock were found to cause significant cardiac contractility depression [100].

In a study to investigate whether IL-1β contributes to LPS-induced dysfunction of multidrug resistance-associated protein 2 [Mrp2], diminished Mrp2 protein expression and activity, as well as its internalization to intracellular domains following exposure to LPS, was partially diminshed after *in vivo* immunoneutralization of IL-1β, which hypothesize that it may contribute to the decreased of expression of Mrp2 at the brush border membrane during experimental endotoxemia [101].

The effect of IL- 1ra on the cognitive impairment associated with sepsis was investigated using the CLP model. Such treatment decreased the levels of IL-1β, IL1-6 and TNF-α, decreased blood brain barrier permeability and oxidative parameters in the pre-frontal cortex, hippocampus and striatum [102]. Recently, the effect of IL-1β on reversing the immune paralysis in late-phase sepsis and increasing survivability was investigated where it was reported to increase survival, numbers of BMCs and liver immune cells [103].

Interleukin-6

Interleukin-6 [also known as interferon-β2] is a pleiotropic interleukin. [104]. It is excessively produced during chronic inflammatory diseases, such as rheumatoid arthritis [RA], and hyper- inflammation, such as cytokine storms [105]. IL-6 receptors consist of two subunits: CD126 and CD130 [gp130] [104]. IL-6 receptor is expressed by several cell types, such as B and T lymphocytes, monocytes/macrophages, and in turn, boosts their functionality [106]. The concentration of IL-6 increases following exposure to bacterial products in the early stages of infection [107].

High levels of IL-6 in septic patients were found to be correlated with increased mortality [108, 109]. Anti-inflammatory effects of IL-6 also were reported which include inhibition of the release of TNF-α and IL-1 [110] and increasing the levels of anti-inflammatory mediators in circulation such as IL-1Ra, sTNFRs, IL-10, TGF-β, and cortisol [111-113]. The advantage of being elevated for a longer period of time than TNF or IL-1β made IL-6 the most extensively studied as a potential biomarker [114].

In the CLP model in mice, prophylactic administration of anti-interleukin-6 antibodies effectively reversed the gastrointestinal motility disturbances and disturbed colonic barrier function that occurs during sepsis. Serum and colonic proinflammatory cytokines levels were lowered with the anti-interleukin-6 antibodies [115]. Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody has been proved successfully against rheumatoid arthritis, juvenile idiopathic arthritis and Castleman disease [116]. In a recent study using the CLP model of sepsis, treatment with tocilizumab alleviated acute lung and kidney injury associated with sepsis and improved survival of septic rats. Such effects were correlated with up-regulated P-glycoprotein [P-gp] expression in pulmonary and renal tissues, inhibition of

NF-κB activation and attenuation of JNK signaling pathway [117].

Interleukin-12

The heterodimeric cytokine; interleukin-12 [IL-12] is structurally related to the IL-6 cytokine family and IL-12 [IL-12p70], consisting of a p35 and a p40 subunit [47-49].

IL-12 links innate and adaptive immune responses either indirectly by NK cell activation or directly through activating CD4+ and CD8+ T cells [118]. IL-12 was found to be higher in survivors of sepsis and vice versa unlike, IL-6, IL-10 and TGFβ1 levels that were higher than IL-12 in the non-survivor group [119].

Administration of a polyclonal IL-12 Ab has been reported to increase survival of mice after CLP or i.p. injection of live *E. coli* *[120, 121]*. But, the administration of anti-IL-12 antiserum was reported to increase the bacterial load following CLP or i.p. administration of *E. coli*, indicating that IL-12 has an effective antibacterial role [122, 123]. Also, in another study to investigate the role of IL-12 on the host defense during polymicrobial sepsis using the CLP model, IL-12 knockout mice showed higher susceptibility to sepsis manifested as higher serum TNF-α and lung neutrophil infiltration which was similar to that of the wild type mice. Such effects were correlated with diminishing the systemic IFN-γ synthesis, decrease of microbicidal activities of their neutrophils, phagocytosis and NO production [124].

Cardiac dysfunction is a well-known serious complication of sepsis [125]. A recent study suggested that IL-12p35 [Il12a] may be considered an important target during the management of such complications as its deletion worsened CLP-induced cardiac dysfunction [126].
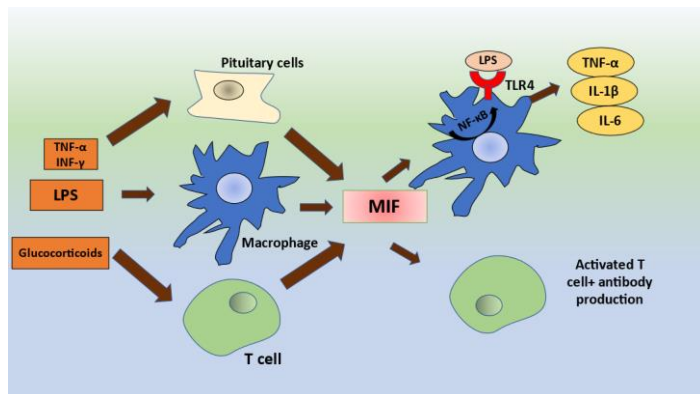

Figure.3: MIF release and action
MIF release from macrophages is triggered by microbial products such as LPS and by glucocorticoids. MIF then acts on immune cells to produce antibodies and upregulate the expression of TLR.

MIF: Macrophage Migration inhibitory factor, LPS: Lipopolysaccharide, TNF-α: Tumor Necrosis Factor- alpha, IL-1β: Interleukin-1 beta, IL-6: Interleukin -6, TLR-4: Toll Like Receptor-4, NF-κB: Nuclear Factor Kappa- b. INF-γ: Interferon-gamma

Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor [MIF] is a pleiotropic cytokine that contributes to the pathogenesis of severe sepsis, ARDS, and autoimmune diseases owing to its pro-inflammatory and immunomodulatory properties. The poor prognosis and severity of such diseases are correlated with the high levels of MIF [32, 127]. MIF regulates the initial immune response which initiates and exaggerates acute respiratory distress syndrome and sepsis [127-129].

Upon induction of its secretion by glucocorticoids during stress, MIF acts as a pro-inflammatory cytokine and a stress response mediator. It acts to impair the eradication of activated monocytes/macrophages by apoptosis, so the inflammatory response remains sustained and so the production of prostaglandins, matrix metalloproteinases and nitric oxide [127, 130]. Proinflammatory mediators such as TNF, IFN-γ and C5a, bacterial endotoxin and exotoxin induce neutrophils to secrete MIF [131] [Figure 3].

MIF-induced autophagy had a crucial role in thrombin-induced endothelial hyperpermeability. Inhibition of MIF or blocking autophagy was effective to reduce mortality in septic mice through attenuation of vascular permeability and leakage [132]. MIF levels were found to be higher in sepsis than in noninfectious systemic inflammation [133, 134]. MIF can predict the prognosis and severity of the disease as it was found to be higher in groups with poor prognosis [135].

In models of polymicrobial peritonitis and mice infected with E. coli, serum and peritoneal fluid MIF levels were found to be high and mice survival was enhanced when treated with anti-MIF antibodies. Same results were obtained using the CLP model even if the anti-MIF antibodies were administered 8 h following the induction of sepsis [136]. Anti-MIF antibodies attenuated TNF-α production and neutralized MIF activity and protected mice from endotoxic shock. Likewise, MIF -knockout mice when compared with wild-type mice, showed less plasma levels of TNFα and were protected against lethal doses of staphylococcal enterotoxin B and LPS [137].

MIF was identified to have tautomerase activity [138]. Such activity was suggested to have potential in the management of the multi-organ dysfunction syndrome following trauma and/or hemorrhage [139]. Treatment with ISO-1, a small molecular weight inhibitor that inhibits of MIF`s tautomerase activity, following the CLP model by 24 h resulted in a higher survival in rats. Specific inhibition of MIF tautomerase activity also showed less NF-κB activation and TNF production in LPS-treated macrophages [140]. Reduction of serum MIF was used as a strategy to reduce sepsis-associated mortality. Continuous renal replacement therapy was found to be an effective strategy to reduce the high serum level of MIF [141].

Interferon-gamma

Interferon gamma [IFN-γ], is a homodimeric protein [56, 57]. Mice deficient of IFN-γ or IFN-γR are more resistant to LPS-induced responses [142, 143]. Systemic administration of IFN-γ decreased survival and aggravates systemic inflammation following induction of sepsis using the CLP model [144]. Also, blockade of IFN-γ improved survival after induction of sepsis using the LPS or CLP model [145, 146]. Several studies have demonstrated that NKT cells promote LPS- or CLP-induced sepsis in mice through the production of IFN-γ [147, 148].

Much higher mortality in patients with sepsis is associated with monocytic deactivation, which is characterized by evident reduced HLA-DR expression of monocytes, a marked reduction of their capacity to produce LPS-induced TNF-α *in vitro,* and loss of antigen-presenting capacity; the well-known "immunoparalysis" phenomenon [149, 150]. Upon application of IFN-γ to septic patients, their monocytes restored the deficient HLA-DR expression and *in vitro* LPS-induced TNF-α secretion. Restoration of the function of monocytes resulted in clearance of sepsis in eight of nine patients [149].

Natural killer cell-derived IFN-γ facilitates the activation of myeloid cells to augment phagocytosis, respiratory burst,

microbial killing. IFN-γ-induced cytokines secretion results in a positive feedback loop that amplifies infection-induced activation of NK cells and myeloid cells. Although these interactions facilitate beneficial antimicrobial functions among macrophages and neutrophils, excessive cytokines amplify inflammation during systemic infection [151].

4. Anti-Inflammatory Cytokines

Interleukin-10

Interleukin [IL]-10 is a potent immunoregulatory molecule and was originally known as cytokine synthesis inhibitory factor produced by T-helper type 2 cells that inhibit T-helper 1 function [63]. Also, IL-10 is associated with the down-regulation of key signaling receptors on antigen-presenting cells such as CD40, CD80, CD86, and MHC II, decreased Mac-1 expression [152], the maintenance of FoxP3 expression in regulatory T cells.

The proinflammatory effects of IL-10 were previously documented in many clinical trials for the treatment of patients with rheumatoid arthritis [153] and volunteers with experimental endotoxemia [154]. Increased IL-10 levels were correlated with sepsis score and may be an indicator of poor patient recovery and high risk for organ dysfunction and fatal outcome [155-157]. A later study conducted by Frencken et al. compromised 708 patients in the ICU with severe sepsis or septic shock showed that mortality is associated with higher IL-10 levels [158]

In a CLP model of sepsis in rodents, systemic administration of high-dose of IL-10 did not affect outcome [159] but also suppressed the immune response to *Pseudomonas pneumonia* in another study using CLP model in mice [160]. Systemic administration of recombinant human IL-10 caused decreased inflammatory response in human endotoxemia and showed no hemodynamic benefits [154].

AS101, an inhibitor of IL-10 expression administered 12 h following sepsis induction increased MHC II expression on APCs, T cell IFN-γ production, and bacterial clearance also decreased tissue damage and so increased the survival [161]. The neutralization of IL-10 resulted in a decrease in the percentages of regulatory T [Tregs] cells in CD4$^+$ T cells, restored the percentages of CD4$^+$ T cells in spleen MNCs, and improved survival rates in septic mice [68]. On the other hand, neutralizing antibodies that block IL-10 resulted in increased neutrophil accumulation and decreased survival [64], which may indicate that the timing for IL-10 neutralization is critical to enhance the host response during sepsis.

Interleukin-10/lymphocyte ratio [IL10LCR] may be a beneficial biomarker for sepsis-induced immunosuppression as its level is significantly associated with the severity and outcome [162].

A recent study conducted by Jensen, McGonagill et al, found that NK cells promote survival by limiting the scope and duration of the cytokine storm. Specifically, NK cell-derived IL-10 which is pivotal for survival during sepsis [163].

Transforming Growth Factor-beta

Transforming growth factor-beta [TGF-β], a cytokine with broad immunosuppressive functions that is pivotal for the resolution of inflammation during tissue injury [164]. Significant induction of TGF-β in mice is evident during the septic response, and TGF-β has been shown to contribute to endotoxin desensitization of monocytes [66, 67]. Specifically, TGF-β inhibits IL-1β and TNF production from monocytes [165, 166]. Furthermore, the TGF-β1 signal was found to be partly involved in the apoptosis of CD4$^+$CD25$^-$ T cells promoted by CD4$^+$CD25$^+$ Tregs [167].

Another study conducted by Nullens et al. demonstrated that lymphocyte depletion occurred in all tissues examined [spleen, mesenteric lymph node, Ileum, colon] at day seven, correlating with increased levels of IL-10 and TGF-β in a murine sepsis model [168]. Anti-TGF-β blocking antibody causes a decrease in Treg cell numbers in the lung tissues which suggests that accumulation of Tregs in the lung tissues- that contributes to immunosuppression and increased susceptibility to secondary infection- is associated with TGF-β [169].

Interleukin-4

A highly pleiotropic cytokine was initially identified as a B-cell differentiation factor, as well as a B-cell stimulatory factor [170]. IL-4 is produced by T cells, mast cells, and basophils and can induce the expression of other anti-inflammatory mediators, including IL-1ra and TNF soluble receptors from monocytes [69-72]. Protective, as well as deleterious effects of IL-4, were reported in *Staphylococcus aureus*-induced murine sepsis, which were shown to be dependent on the host's genetic map [171].

Interleukin-4 suppresses the polarizing and differentiating of Th1 cells. It also has a crucial role in B cell differentiation, thus promoting a Th2 mediated response [172].

In animal models of sepsis. IL-4 suppressed cell-mediated immunity and so death through activation of the Stat 6 pathway [173]. In 56 cases of patients with severe trauma who developed sepsis, showed no correlation between il-4 and severity neither outcome of sepsis [174].

5. Trials targeting cytokines

Targeting Tumor Necrosis Factor-alpha, Interleukin- 1, Interleukin-17 and Interleukin-18

In experimental studies of sepsis, blocking TNF-α effects showed promising results as it effectively reduced both morbidity and mortality [175]. Other experimental studies also showed the same results [176-178]. That is why the anti-cytokine therapy was assumed to have some efficacy against sepsis. However, such results could not be replicated in the clinical trials, but such therapy showed deleterious effects. In a randomized, double-blind study, when septic patients were dosed with recombinant soluble TNF-α receptor, it did not enhance survivability but high lead to high mortality rates [179]. Additionally, the use of anti-TNF-α therapy has been associated with an elevated risk of infections [180].

In a phase III, randomized, double-blinded, placebo-controlled, multicenter trial, rhIL-1ra failed to reduce mortality when compared with standard therapy, suggesting that overproduction of either pro-inflammatory mediators [IL-1α and IL-1β] or anti-inflammatory cytokines [IL-1ra] might lead to organ dysfunction and even death [181].

Treatment of septic mice with anti-IL-17A increased chemokines and HMGB-1 and reduced serum levels of proinflammatory mediators and increased survival rates when administered 12hr following CLP [182]. However, A prospective cohort study that included 60 patients with severe sepsis revealed that IL-17 was not detected [183]. Multiple studies have demonstrated that high plasma levels of IL-18 are correlated with poor clinical outcomes in severe septic and inflammatory cases [184, 185]. Experimental data hypothesize such biological neutralization may have a promising therapeutic efficacy in the treatment of sepsis [186].

Immune-augmentation strategies:

Although multiple immunomodulators have been tried to reduce levels of targeted cytokines and showed promising results in experimental trials but they failed to show the same effects in

clinical trials but also increased mortality. Such failure may be due to the fact that septic patients die later in the course of sepsis when the phase of immunosuppression. During such phase, the innate and adaptive immune responses are impaired. In addition, enhanced apoptosis and dysfunction of lymphocytes, impaired phagocyte functions, monocytic deactivation with diminished HLA class II surface expression, and altered ex vivo cytokine production occur [12, 187]. So, the term "immunoparalysis" emerged to describe the inability of the host to defend himself against infections [188].

Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor [GMCSF] is a potent cytokine with immunostimulatory effects through potentiation of antimicrobial host defense as it improves survival, proliferation, differentiation, phagocytosis of neutrophils and monocytes/macrophages. And also, through enhancing migration and adhesion of neutrophils [189]. This effect has been illustrated in a randomized, un-blinded, placebo-controlled prospective study where GM-CSF group showed a significantly higher increase in total leukocyte counts which indicated increased rates of infection clearance in addition to the clinical improvement. But, still no difference in mortality [190]. Reduced survival in sepsis was found to be associated with prolonged downregulation of low levels of monocytic HLA-DR [mHLA-DR] [187]. In a prospective, randomized, double-blind, placebo-controlled, multicenter trial; GM-CSF was a safe and effective measure to restore mHLA-DR expression and to increase the numbers of neutrophils and monocytes, also the time of mechanical ventilation and hospital/ intensive care unit stay was shortened [191]. Regardless of these desirable effects in many clinical outcomes, 28-day mortality was not lowered.

Interleukin 7 and interleukin 15

Cells from septic patients treated ex vivo with rhIL-7 significantly showed improved lymphocyte functionality which was manifested as CD4^{+} and CD8^{+} lymphocyte proliferation, B cell lymphoma 2 induction, IFN-γ production, and STAT5 phosphorylation. Such results supported its ability to restore normal lymphocyte functions during sepsis [192]. IL-7 improved survival significantly in CLP-induced sepsis followed by P. aeruginosa pneumonia. Regarding the high mortality associated with secondary P. aeruginosa pneumonia, IL-7 increased the number of immune effector cells in the lung and spleen, increased IL-17-, IFN-γ-, and TNF-α-producing ILCs and CD8 T cells in lung tissues which are essential for the host defense against sepsis and P. aeruginosa pneumonia. In addition, NF-κB and STAT3 pathways were induced in the lungs [193]. In a phase 2 trial, administration of recombinant human IL-7 [CYT107] in patients with septic shock and severe lymphopenia improved the marked loss of CD4^{+} and CD8^{+} immune effector cells, which is considered the key mechanism in morbidity and mortality during sepsis [194].

Serum levels of IL-15 were found to be an indicator of the prognosis of septic patients following emergent abdominal surgery as it correlated with the duration of SIRS and organ dysfunction. It correlated positively with creatinine levels and negatively with the PaO2/FiO2 [195].

On the other hand, in a rat model of CLP-induced sepsis, recombinant IL-15 raised the Levels of IL-15 and IFN-γ in peripheral blood of septic rats, in addition to the numbers of peripheral T cells and natural killer [NK] cells, which resulted in enhanced survival [196].

6.Cytokines and Covid-19

The severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] outbreak, which was first appeared in Wuhan, China, in December 2019, has had a tremendous influence on China and the whole world [197]. Viral sepsis was hypothesized to be pivotal to the disease mechanism of COVID-19 [198]. Management of the cytokine storm was suggested to be critical for rescuing patients with severe COVID-19. Immunomodulators and cytokine antagonists for early control of the cytokine storm are crucial to increase the survival rate of patients with COVID-19 [199-201].

In a retrospective cohort study of patients with consecutively COVID-19, moderate-to-severe ARDS, and hyperinflammation, the high-dose intravenous anakinra; an IL-1 receptor antagonist [IL-1ra] treated group showed a higher survival compared to the standard treated group, reduction in serum C-reactive protein and progressive improvements in respiratory function [202]. Despite the limitations of this study; the relatively small size of the cohorts and the need for more follow-up to investigate the long-term outcomes, but such results still seem to be promising.

In a retrospective observational study conducted by Capra, De Rossi et al., 85 consecutive patients were administered the IL-6 blocker; tocilizumab to treat COVID-19, showed significantly greater survival rate when compared to control patients and improved respiratory function [203]. McElvaney, Curley et al. reported that groups with a high CRP might get more benefit of the anti-IL-6 therapy regarding the role of IL-6 as a CRP inducer [204].

The risk of patient's requirement to ICU in COVID-19 patients was found to increase by 8,8-fold when it was accompanied by elevated MIF levels [205]. Also, MIF is considered an early biomarker to predict the response to the early initiated ICU treatment in critically ill patients with COVID-19 disease [206].

Conclusion

Sepsis remains to be one of the global serious health problems. Many factors contributed to the lack of such effective strategies in clinical settings. Until now, the use of irrelevant models in sepsis research resulted in the emergence of non-targeted and incapable drugs for managing septic cases. This could be explained in the light of the fact that immune response varies greatly between species, also during such experiments; drugs are dosed at a certain time before or after induction of sepsis which is considered impossible to be clinically determined exactly. Heterogenicity in septic patients is another factor contributing to such detach between experimental trials and clinical cases which may be correlated to the difference in sepsis sources, different levels of inflammation, and yet different responses to treatment. Although all anti-cytokine treatments were found to be promising in murine models, they did not reveal any change neither in the overall survival nor in the patient outcome. Moreover, they increased mortality in some cases. So lately, the chronic immunoparalytic phase became the focus of interest as the cause of most sepsis-associated deaths which is characterized by a decrease in pro-inflammatory cytokine levels and leukopenia, increased risk of infection by opportunistic pathogens, and subsequently death. During such phase, immunostimulatory adjuvant therapies reverse the immunoparalysis that takes place aiming to increase the number of functional leukocytes and target diminished apoptosis. In other promising approaches, blocking the already self-sustaining inflammatory cascade is not the target but limiting what is ultimately killing patients; like vascular-induced tissue damage. Targeting Slit-Robo4 seemed to be effective in the endotoxemia model to reduce the levels of

circulating inflammatory cytokines e levels of circulating inflammatory cytokines. Upregulation of PD-1 on T lymphocytes and particularly PD-L1 on APC's is another contributing pathway in immune tolerance. Blocking PD-1 and PD-L1 antagonizes the interaction between the two molecules which in turn retrieves T cell function which is of significant importance in countering such infectious diseases.

References

[1] Fleischmann C, Scherag A, Adhikari NK, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current estimates and limitations. American journal of respiratory and critical care medicine. 2016;193[3]:259-72.

[2] Durning MV. Sepsis: A Review for Home Healthcare Clinicians. Home Healthcare Now. 2020;38[4]:188-92.

[3] Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. New England Journal of Medicine. 2010;362[23]:2155-65.

[4] Siegel R. M a J, Zou Z, et al. Cancer statistics, 2014. CA Cancer J Clin. 2014;64[1]:9-29.

[5] Friedman G, Silva E, Vincent J-L. Has the mortality of septic shock changed with time? Critical care medicine. 1998;26[12]:2078-86.

[6] Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5[1]:4-11.

[7] Hübner MP, Layland LE, Hoerauf A. Helminths and their implication in sepsis–a new branch of their immunomodulatory behaviour? Pathogens and disease. 2013;69[2]:127-41.

[8] Florescu DF, Kalil AC. The complex link between influenza and severe sepsis. Virulence. 2014;5[1]:137-42.

[9] Liang SY. Sepsis and other infectious disease emergencies in the elderly. Emergency Medicine Clinics. 2016;34[3]:501-22.

[10] Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis and septic shock: current treatment strategies and new approaches. The Eurasian journal of medicine. 2017;49[1]:53.

[11] Ding R, Meng Y, Ma X. The central role of the inflammatory response in understanding the heterogeneity of sepsis-3. BioMed research international. 2018;2018.

[12] Cohen J. The immunopathogenesis of sepsis. Nature. 2002;420[6917]:885-91.

[13] Hansen JD, Vojtech LN, Laing KJ. Sensing disease and danger: a survey of vertebrate PRRs and their origins. Developmental & Comparative Immunology. 2011;35[9]:886-97.

[14] Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. Clinical microbiology reviews. 2009;22[2]:240-73.

[15] Chen GY, Nuñez G. Sterile inflammation: sensing and reacting to damage. Nature Reviews Immunology. 2010;10[12]:826-37.

[16] van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. Nature Reviews Immunology. 2017;17[7]:407-20.

[17] Baccala R, Gonzalez-Quintial R, Lawson BR, Stern ME, Kono DH, Beutler B, et al. Sensors of the innate immune system: their mode of action. Nature Reviews Rheumatology. 2009;5[8]:448-56.

[18] Junt T, Barchet W. Translating nucleic acid-sensing pathways into therapies. Nature Reviews Immunology. 2015;15[9]:529-44.

[19] Yan J, Li S, Li S. The role of the liver in sepsis. International reviews of immunology. 2014;33[6]:498-510.

[20] Armstrong L, Medford A, Hunter K, Uppington K, Millar A. Differential expression of Toll-like receptor [TLR]-2 and TLR-4 on monocytes in human sepsis. Clinical & Experimental Immunology. 2004;136[2]:312-9.

[21] Härter L, Mica L, Stocker R, Trentz O, Keel M. Increased expression of toll-like receptor-2 and-4 on leukocytes from patients with sepsis. Shock. 2004;22[5]:403-9.

[22] Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity. 2011;34[5]:637-50.

[23] Annane D, Bellissant E, Cavaillon J-M. Septic shock. The Lancet. 2005;365[9453]:63-78.

[24] Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent J-L. Sepsis and septic shock. Nature reviews Disease primers. 2016;2[1]:1-21.

[25] Steinhagen F, Rodriguez LG, Tross D, Tewary P, Bode C, Klinman DM. IRF5 and IRF8 modulate the CAL-1 human plasmacytoid dendritic cell line response following TLR9 ligation. European journal of immunology. 2016;46[3]:647-55.

[26] Blackwell T, Christman J. Sepsis and cytokines: current status. British journal of anaesthesia. 1996;77[1]:110-7.

[27] Aikawa N. Cytokine storm in the pathogenesis of multiple organ dysfunction syndrome associated with surgical insults. Nihon Geka Gakkai Zasshi. 1996;97[9]:771.

[28] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. New England Journal of Medicine. 2001;345[19]:1368-77.

[29] Denk S, Perl M, Huber-Lang M. Damage-and pathogen-associated molecular patterns and alarmins: keys to sepsis? European Surgical Research. 2012;48[4]:171-9.

[30] Atsumi T, Cho Y-R, Leng L, McDonald C, Yu T, Danton C, et al. The proinflammatory cytokine macrophage migration inhibitory factor regulates glucose metabolism during systemic inflammation. The Journal of Immunology. 2007;179[8]:5399-406.

[31] Mlinar B, Marc J. New insights into adipose tissue dysfunction in insulin resistance. Clinical Chemistry and Laboratory Medicine [CCLM]. 2011;49[12]:1925-35.

[32] Emonts M, Sweep FC, Grebenchtchikov N, Geurts-Moespot A, Knaup M, Chanson AL, et al. Association between high levels of blood macrophage migration inhibitory factor, inappropriate adrenal response, and early death in patients with severe sepsis. Clinical infectious diseases. 2007;44[10]:1321-8.

[33] Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacology & therapeutics. 2011;130[2]:226-38.

[34] Levi M, van der Poll T. Inflammation and coagulation. Critical care medicine. 2010;38:S26-S34.

[35] Hack CE, Aarden LA, Thus LG. Role of cytokines in sepsis. Advances in immunology. 66: Elsevier; 1997. p. 101-95.

[36] Junger WG, Hoyt DB, Liu FC, Loomis WH, Coimbra R. Immunosuppression after endotoxin shock: the result of multiple anti-inflammatory factors. Journal of Trauma and Acute Care Surgery. 1996;40[5]:702-9.

[37] Grivennikov SI, Tumanov AV, Liepinsh DJ, Kruglov AA, Marakusha BI, Shakhov AN, et al. Distinct and nonredundant in vivo functions of TNF produced by t cells and macrophages/neutrophils: protective and deleterious effects. Immunity. 2005;22[1]:93-104.

[38] Aitken SL, Corl CM, Sordillo LM. Pro-inflammatory and pro-apoptotic responses of TNF-α stimulated bovine mammary endothelial cells. Veterinary Immunology and Immunopathology. 2011;140[3-4]:282-90.

[39] Van Kampen C, Mallard BA. Regulation of bovine intercellular adhesion molecule 1 [ICAM-1] and vascular cell adhesion molecule 1 [VCAM-1] on cultured aortic endothelial cells. Veterinary immunology and immunopathology. 2001;79[1-2]:129-38.

[40] Kim YS, Ahn Y, Hong MH, Joo SY, Kim KH, Sohn IS, et al. Curcumin attenuates inflammatory responses of TNF-α-stimulated human endothelial cells. Journal of cardiovascular pharmacology. 2007;50[1]:41-9.

[41] MacNaul K, Hutchinson N. Differential expression of iNOS and cNOS mRNA in human vascular smooth muscle cells and endothelial cells under normal and inflammatory conditions. Biochemical and biophysical research communications. 1993;196[3]:1330-4.

[42] Kaplanski G, Farnarier C, Kaplanski S, Porat R, Shapiro L, Bongrand P, et al. Interleukin-1 induces interleukin-8 secretion from endothelial cells by a juxtacrine mechanism. 1994.

[43] Pruitt JH, Copeland 3rd E, Moldawer LL. Interleukin-1 and interleukin-1 antagonism in sepsis, systemic inflammatory response syndrome, and septic shock. Shock [Augusta, Ga]. 1995;3[4]:235-51.

[44] Cho J-H, Cho SB, editors. An architecture for real-time hardware co-simulation of edge detection in image processing using Prewitt edge operator. 2014 International Conference on Electronics, Information and Communications [ICEIC]; 2014: IEEE.

[45] Park JY, Pillinger MH. Interleukin-6 in the pathogenesis of rheumatoid arthritis. Bulletin of the NYU hospital for joint diseases. 2007;65:S4-10.

[46] Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. European journal of immunology. 2010;40[7]:1830-5.

[47] Jones LL, Vignali DA. Molecular interactions within the IL-6/IL-12 cytokine/receptor superfamily. Immunologic research. 2011;51[1]:5.

[48] Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. Nature Reviews Immunology. 2003;3[2]:133-46.

[49] Sun L, He C, Nair L, Yeung J, Egwuagu CE. Interleukin 12 [IL-12] family cytokines: Role in immune pathogenesis and treatment of CNS autoimmune disease. Cytokine. 2015;75[2]:249-55.

[50] Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nature immunology. 2015;16[4]:343-53.

[51] Adib-Conquy M, Cavaillon J-M. Stress molecules in sepsis and systemic inflammatory response syndrome. FEBS letters. 2007;581[19]:3723-33.

[52] Morand EF. New therapeutic target in inflammatory disease: macrophage migration inhibitory factor. Internal medicine journal. 2005;35[7]:419-26.

[53] Chuang C-C, Chuang Y-C, Chang W-T, Chen C-C, Hor L-I, Huang A-M, et al. Macrophage migration inhibitory factor regulates interleukin-6 production by facilitating nuclear factor-kappa B activation during Vibrio vulnificus infection. BMC immunology. 2010;11[1]:1-8.

[54] Cvetkovic I, Stosic-Grujicic S. Neutralization of macrophage migration inhibitory factor—novel approach for the treatment of immunoinflammatory disorders. International immunopharmacology. 2006;6[10]:1527-34.

[55] Calandra T, Froidevaux C, Martin C, Roger T. Macrophage migration inhibitory factor and host innate immune defenses against bacterial sepsis. The Journal of infectious diseases. 2003;187[Supplement_2]:S385-S90.

[56] Ogasawara K, Takeda K, Hashimoto W, Satoh M, Okuyama R, Yanai N, et al. Involvement of NK1+ T cells and their IFN-γ production in the generalized Shwartzman reaction. The Journal of Immunology. 1998;160[7]:3522-7.

[57] Feng CG, Kaviratne M, Rothfuchs AG, Cheever A, Hieny S, Young HA, et al. NK cell-derived IFN-γ differentially regulates innate resistance and neutrophil response in T cell-deficient hosts infected with Mycobacterium tuberculosis. The Journal of Immunology. 2006;177[10]:7086-93.

[58] Heremans H, Billiau A. The potential role of interferons and interferon antagonists in inflammatory disease. Drugs. 1989;38[6]:957-72.

[59] Heremans H, Dillen C, Groenen M, Matthys P, Billiau A. Role of interferon-γ and nitric oxide in pulmonary edema and death induced by lipopolysaccharide. American journal of respiratory and critical care medicine. 2000;161[1]:110-7.

[60] Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annual review of immunology. 2001;19[1]:683-765.

[61] Lyons A, Kelly JL, Rodrick ML, Mannick JA, Lederer JA. Major injury induces increased production of interleukin-10 by cells of the immune system with a negative impact on resistance to infection. Annals of surgery. 1997;226[4]:450.

[62] Fiorentino DF, Bond MW, Mosmann T. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhibits cytokine production by Th1 clones. Journal of Experimental Medicine. 1989;170[6]:2081-95.

[63] de Vries JE. Immunosuppressive and anti-inflammatory properties of interleukin 10. Annals of medicine. 1995;27[5]:537-41.

[64] Scott MJ, Hoth JJ, Turina M, Woods DR, Cheadle WG. Interleukin-10 suppresses natural killer cell but not natural killer T cell activation during bacterial infection. Cytokine. 2006;33[2]:79-86.

[65] Dang PM-C, Elbim C, Marie J-C, Chiandotto M, Gougerot-Pocidalo M-A, El-Benna J, et al. Anti-inflammatory effect of interleukin-10 on human neutrophil respiratory burst involves inhibition of GM-CSF-induced p47PHOX phosphorylation through a decrease in ERK1/2 activity. The FASEB journal. 2006;20[9]:1504-6.

[66] Randow F, Syrbe U, Meisel C, Krausch D, Zuckermann H, Platzer C, et al. Mechanism of endotoxin desensitization: involvement of interleukin 10 and transforming growth factor beta. Journal of Experimental Medicine. 1995;181[5]:1887-92.

[67] Ahmad S, Choudhry MA, Shankar R, Sayeed MM. Transforming growth factor-β negatively modulates T-cell responses in sepsis. FEBS letters. 1997;402[2-3]:213-8.

[68] Hiraki S, Ono S, Tsujimoto H, Kinoshita M, Takahata R, Miyazaki H, et al. Neutralization of interleukin-10 or transforming growth factor-β decreases the percentages of CD4+ CD25+ Foxp3+ regulatory T cells in septic mice, thereby leading to an improved survival. Surgery. 2012;151[2]:313-22.

[69] te Velde AA, Huijbens R, Heije K, de Vries JE, Figdor CG. Interleukin-4 [IL-4] inhibits secretion of IL-1 beta, tumor necrosis factor alpha, and IL-6 by human monocytes. 1990.

[70] Standiford T, Strieter R, Chensue S, Westwick J, Kasahara K, Kunkel S. IL-4 inhibits the expression of IL-8 from stimulated human monocytes. The Journal of Immunology. 1990;145[5]:1435-9.

[71] Al-Ramadi BK, Meissler Jr JJ, Huang D, Eisenstein TK. Immunosuppression induced by nitric oxide and its inhibition by interleukin-4. European journal of immunology. 1992;22[9]:2249-54.

[72] Jenkins JK, Arend WP. Interleukin 1 receptor antagonist production in human monocytes is induced by IL-1α, IL-3, IL-4 and GM-CSF. Cytokine. 1993;5[5]:407-15.

[73] Paul WE. Interleukin-4: a prototypic immunoregulatory lymphokine. Blood. 1991;77[9]:1859-70.

[74] Sone S, Yanagawa H, Nishioka Y, Orino E, Bhaskaran G, Nii A, et al. Interleukin-4 as a potent down-regulator for human alveolar macrophages capable of producing tumour necrosis factor-alpha and interleukin-1. European Respiratory Journal. 1992;5[2]:174-81.

[75] Opal SM, DePalo VA. Anti-inflammatory cytokines. Chest. 2000;117[4]:1162-72.

[76] Vannier E, Miller LC, Dinarello CA. Coordinated antiinflammatory effects of interleukin 4: interleukin 4 suppresses interleukin 1 production but up-regulates gene expression and synthesis of interleukin 1 receptor antagonist. Proceedings of the National Academy of Sciences. 1992;89[9]:4076-80.

[77] Kumar V. Inflammasomes: Pandora's box for sepsis. Journal of inflammation research. 2018;11:477.

[78] Weber GF, Chousterman BG, He S, Fenn AM, Nairz M, Anzai A, et al. Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis. Science. 2015;347[6227]:1260-5.

[79] Carswell EA, Old LJ, Kassel R, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proceedings of the National Academy of Sciences. 1975;72[9]:3666-70.

[80] Ghosh S. Anti-TNF therapy in Crohn's disease. Inflammatory Bowel Disease: Crossroads of Microbes, Epithelium and Immune Systems. 2005;263:193.

[81] Seymour H, Worsley A, Smith J, Thomas S. Anti-TNF agents for rheumatoid arthritis. British journal of clinical pharmacology. 2001;51[3]:201-8.

[82] Coates LC, Marzo-Ortega H, Bennett AN, Emery P. Anti-TNF therapy in ankylosing spondylitis: insights for the clinician. Therapeutic advances in musculoskeletal disease. 2010;2[1]:37-43.

[83] Esposito E, Cuzzocrea S. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. Current medicinal chemistry. 2009;16[24]:3152-67.

[84] Parameswaran N, Patial S. Tumor necrosis factor-α signaling in macrophages. Critical Reviews™ in Eukaryotic Gene Expression. 2010;20[2].

[85] Goldie AS, Fearon KC, Ross JA, Barclay GR, Jackson RE, Grant IS, et al. Natural cytokine antagonists and endogenous antiendotoxin core antibodies in sepsis syndrome. Jama. 1995;274[2]:172-7.

[86] Kirchner S, Boldt S, Kolch W, Haffner S, Kazak S, Janosch P, et al. LPS resistance in monocytic cells caused by reverse signaling through transmembrane TNF [mTNF] is mediated by the MAPK/ERK pathway. Journal of leukocyte biology. 2004;75[2]:324-31.

[87] Ermert M, Pantazis C, Duncker H-R, Grimminger F, Seeger W, Ermert L. In situ localization of TNFα/β, TACE AND TNF receptors TNF-R1 and TNF-R2 in control and LPS-treated lung tissue. Cytokine. 2003;22[3-4]:89-100.

[88] Beutler B, Milsark I, Cerami A. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effect of endotoxin. Science. 1985;229[4716]:869-71.

[89] Eichacker PQ, Parent C, Kalil A, Esposito C, Cui X, Banks SM, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. American journal of respiratory and critical care medicine. 2002;166[9]:1197-205.

[90] Lorente JA, Marshall JC. Neutralization of tumor necrosis factor in preclinical models of sepsis. Shock. 2005;24:107-19.

[91] Eskandari MK, Bolgos G, Miller C, Nguyen DT, DeForge LE, Remick DG. Anti-tumor necrosis factor antibody therapy fails to prevent lethality after cecal ligation and puncture or endotoxemia. The Journal of Immunology. 1992;148[9]:2724-30.

[92] Echtenacher B, Weigl K, Lehn N, Männel DN. Tumor necrosis factor-dependent adhesions as a major protective mechanism early in septic peritonitis in mice. Infection and immunity. 2001;69[6]:3550-5.

[93] Belisle SE, Tisoncik JR, Korth MJ, Carter VS, Proll SC, Swayne DE, et al. Genomic profiling of tumor necrosis factor alpha [TNF-α] receptor and interleukin-1 receptor knockout mice reveals a link between TNF-α signaling and increased severity of 1918 pandemic influenza virus infection. Journal of virology. 2010;84[24]:12576-88.

[94] Dinarello CA, Renfer L, Wolff SM. Human leukocytic pyrogen: purification and development of a radioimmunoassay. Proceedings of the National Academy of Sciences. 1977;74[10]:4624-7.

[95] Kurt A, Aygun AD, Godekmerdan A, Kurt A, Dogan Y, Yilmaz E. Serum IL-1β, IL-6, IL-8, and TNF-α levels in early diagnosis and management of neonatal sepsis. Mediators of inflammation. 2007;2007.

[96] Fida NM, AL-MUGHALES J, Farouq M. Interleukin-1α, interleukin-6 and tumor necrosis factor-α levels in children with sepsis and meningitis. Pediatrics international. 2006;48[2]:118-24.

[97] Goldbach-Mansky R. Current status of understanding the pathogenesis and management of patients with NOMID/CINCA. Current rheumatology reports. 2011;13[2]:123-31.

[98] Agostini L, Martinon F, Burns K, McDermott MF, Hawkins PN, Tschopp J. NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle-Wells autoinflammatory disorder. Immunity. 2004;20[3]:319-25.

[99] Dinarello CA, editor Targeting the pathogenic role of interleukin 1β in the progression of smoldering/indolent myeloma to active disease. Mayo Clinic Proceedings; 2009: Elsevier.

[100] Kumar A, Krieger A, Symeoneides S, Kumar A, Parrillo JE. Myocardial dysfunction in septic shock: Part II. Role of cytokines and nitric oxide. Journal of cardiothoracic and vascular anesthesia. 2001;15[4]:485-511.

[101] Arana MR, Dominguez CJ, Zecchinati F, Tocchetti GN, Mottino AD, Villanueva SSM. Role of interleukin 1 beta in the regulation of rat intestinal multidrug resistance-associated protein 2 under conditions of experimental endotoxemia. Toxicology. 2020;441:152527.

[102] Mina F, Comim CM, Dominguini D, Cassol-Jr OJ, DallIgna DM, Ferreira GK, et al. Il1-β involvement in cognitive impairment after sepsis. Molecular neurobiology. 2014;49[2]:1069-76.

[103] Guo H-l, Shi F-d, Zhou Q, Liu Q-y, Wang Y-x, Song Y, et al. Interleukin-1β Protection Against Experimental Sepsis in Mice. Inflammation. 2021;44[1]:358-70.

[104] Jones SA, Scheller J, Rose-John S. Therapeutic strategies for the clinical blockade of IL-6/gp130 signaling. The Journal of clinical investigation. 2011;121[9]:3375-83.

[105] Narazaki M, Kishimoto T. The two-faced cytokine IL-6 in host defense and diseases. International journal of molecular sciences. 2018;19[11]:3528.

[106] Sims JE, Smith DE. The IL-1 family: regulators of immunity. Nature Reviews Immunology. 2010;10[2]:89-102.

[107] Jekarl DW, Lee S-Y, Lee J, Park Y-J, Kim Y, Park JH, et al. Procalcitonin as a diagnostic marker and IL-6 as a prognostic marker for sepsis. Diagnostic microbiology and infectious disease. 2013;75[4]:342-7.

[108] Patel R, Deen K, Youngs D, Warwick J, Keighley M. Interleukin 6 is a prognostic indicator of outcome in severe intra-abdominal sepsis. Journal of British Surgery. 1994;81[9]:1306-8.

[109] Pettilä V, Hynninen M, Takkunen O, Kuusela P, Valtonen M. Predictive value of procalcitonin and interleukin 6 in critically ill patients with suspected sepsis. Intensive care medicine. 2002;28[9]:1220-5.

[110] Remick DG, Bolgos G, Copeland S, Siddiqui J. Role of interleukin-6 in mortality from and physiologic response to sepsis. Infection and immunity. 2005;73[5]:2751-7.

[111] Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. American Journal of Physiology-Endocrinology And Metabolism. 2003;285[2]:E433-E7.

[112] Tilg H, Trehu E, Atkins MB, Dinarello CA, Mier JW. Interleukin-6 [IL-6] as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. 1994.

[113] Zhang XL, Topley N, Ito T, Phillips A. Interleukin-6 regulation of transforming growth factor [TGF]-β receptor compartmentalization and turnover enhances TGF-β1 signaling. Journal of Biological Chemistry. 2005;280[13]:12239-45.

[114] Batfalsky A, Lohr A, Heussen N, Neunhoeffer F, Orlikowsky T. Diagnostic value of an interleukin-6 bedside test in term and preterm neonates at the time of clinical suspicion of early-and late-onset bacterial infection. Neonatology. 2012;102[1]:37-44.

[115] Nullens S, Staessens M, Peleman C, Plaeke P, Malhotra-Kumar S, Francque S, et al. Beneficial effects of anti-interleukin-6 antibodies on impaired gastrointestinal motility, inflammation and increased colonic permeability in a murine model of sepsis are most pronounced when administered in a preventive setup. PloS one. 2016;11[4]:e0152914.

[116] Kang S, Tanaka T, Kishimoto T. Therapeutic uses of anti-interleukin-6 receptor antibody. International Immunology. 2014;27[1]:21-9.

[117] Ibrahim YF, Moussa RA, Bayoumi AM, Ahmed A-SF. Tocilizumab attenuates acute lung and kidney injuries and improves survival in a rat model of sepsis via down-regulation of NF-κB/JNK: a possible role of P-glycoprotein. Inflammopharmacology. 2020;28[1]:215-30.

[118] Chaudhry H, Zhou J, Zhong Y, Ali MM, McGuire F, Nagarkatti PS, et al. Role of cytokines as a double-edged sword in sepsis. In vivo. 2013;27[6]:669-84.

[119] Wu H-P, Shih C-C, Lin C-Y, Hua C-C, Chuang D-Y. Serial increase of IL-12 response and human leukocyte antigen-DR expression in severe sepsis survivors. Critical Care. 2011;15[5]:1-9.

[120] Echtenacher B, Freudenberg MA, Jack RS, Männel DN. Differences in innate defense mechanisms in endotoxemia and polymicrobial septic peritonitis. Infection and immunity. 2001;69[12]:7271-6.

[121] Godshall CJ, Lentsch AB, Peyton JC, Scott MJ, Cheadle WG. STAT4 is required for antibacterial defense but enhances mortality during polymicrobial sepsis. Clinical Diagnostic Laboratory Immunology. 2001;8[6]:1044-8.

[122] Zisman DA, Kunkel SL, Strieter RM, Gauldie J, Tsai WC, Bramson J, et al. Anti-interleukin-12 therapy protects mice in lethal endotoxemia but impairs bacterial clearance in murine Escherichia coli peritoneal sepsis. Shock [Augusta, Ga]. 1997;8[5]:349-56.

[123] Steinhauser ML, Hogaboam CM, Lukacs NW, Strieter RM, Kunkel SL. Multiple roles for IL-12 in a model of acute septic peritonitis. The Journal of Immunology. 1999;162[9]:5437-43.

[124] Moreno SE, Alves-Filho JC, Alfaya TM, da Silva JS, Ferreira SH, Liew FY. IL-12, but not IL-18, is critical to neutrophil activation and resistance to polymicrobial sepsis induced by cecal ligation and puncture. The Journal of Immunology. 2006;177[5]:3218-24.

[125] van der Slikke EC, An AY, Hancock RE, Bouma HR. Exploring the pathophysiology of post-sepsis syndrome to identify therapeutic opportunities. EBioMedicine. 2020;61:103044.

[126] Wang Z, Liu M, Di Ye JY, Wang M, Liu J, Xu Y, et al. Il12a Deletion Aggravates Sepsis-Induced Cardiac Dysfunction by Regulating Macrophage Polarization. Frontiers in Pharmacology. 2021;12.

[127] Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. Nature reviews immunology. 2003;3[10]:791-800.

[128] Donnelly SC, Haslett C, Reid PT, Grant IS, Wallace WA, Metz CN, et al. Regulatory role for macrophage migration inhibitory factor in acute respiratory distress syndrome. Nature medicine. 1997;3[3]:320-3.

[129] Tang Y, Qiu S, Jiang F, Yi L, Guo L. Effects of macrophage migration inhibitory factor in pathogenesis of acute respiratory distress syndrome in children. Zhonghua er ke za zhi= Chinese Journal of Pediatrics. 2006;44[5]:356-9.

[130] Cinel I, Opal SM. Molecular biology of inflammation and sepsis: a primer. Critical care medicine. 2009;37[1]:291-304.

[131] Riedemann NC, Guo R-F, Gao H, Sun L, Hoesel M, Hollmann TJ, et al. Regulatory role of C5a on macrophage migration inhibitory factor release from neutrophils. The Journal of Immunology. 2004;173[2]:1355-9.

[132] Chao C-H, Chen H-R, Chuang Y-C, Yeh T-M. Macrophage migration inhibitory factor-induced autophagy contributes to thrombin-triggered endothelial hyperpermeability in sepsis. Shock. 2018;50[1]:103-11.

[133] Jose S, Mukherjee A, Abhyankar MM, Leng L, Bucala R, Sharma D, et al. Neutralization of macrophage migration inhibitory factor improves host survival after Clostridium difficile infection. Anaerobe. 2018;53:56-63.

[134] Pohl J, Hendgen-Cotta UB, Stock P, Luedike P, Rassaf T. Elevated MIF-2 levels predict mortality in critically ill patients. Journal of critical care. 2017;40:52-7.

[135] Toldi J, Nemeth D, Hegyi P, Molnar Z, Solymar M, Farkas N, et al. Macrophage migration inhibitory factor as a diagnostic and predictive biomarker in sepsis: meta-analysis of clinical trials. Scientific reports. 2021;11[1]:1-12.

[136] Calandra T, Echtenacher B, Le Roy D, Pugin J, Metz CN, Hültner L, et al. Protection from septic shock by neutralization of macrophage migration inhibitory factor. Nature medicine. 2000;6[2]:164-70.

[137] Bozza M, Satoskar AR, Lin G, Lu B, Humbles AA, Gerard C, et al. Targeted disruption of migration inhibitory factor gene reveals its critical role in sepsis. The Journal of experimental medicine. 1999;189[2]:341-6.

[138] Rosengren E, Bucala R, Åman P, Jacobsson L, Odh G, Metz CN, et al. The immunoregulatory mediator macrophage migration inhibitory factor [MIF] catalyzes a tautomerization reaction. Molecular medicine. 1996;2[1]:143-9.

[139] Patel NM, Martin L, Yamada N, Oliveira FRMB, Stiehler L, Zechendorf E, et al. The inhibition of Macrophage Migration Inhibitory Factor by ISO-1 attenuates trauma-induced multiorgan dysfunction in rats. medRxiv. 2021.

[140] Al-Abed Y, Dabideen D, Aljabari B, Valster A, Messmer D, Ochani M, et al. ISO-1 binding to the tautomerase active site of MIF inhibits its pro-inflammatory activity and increases survival in severe sepsis. Journal of Biological Chemistry. 2005;280[44]:36541-4.

[141] Pohl J, Papathanasiou M, Heisler M, Stock P, Kelm M, Hendgen-Cotta UB, et al. Renal replacement therapy neutralizes elevated MIF levels in septic shock. Journal of intensive care. 2016;4[1]:1-7.

[142] Shimizu Y, Margenthaler JA, Landeros K, Otomo N, Doherty G, Flye MW. The resistance of P. acnes–primed interferon γ–deficient mice to low-dose lipopolysaccharide-induced acute liver injury. Hepatology. 2002;35[4]:805-14.

[143] Car B, Eng VM, Schnyder B, Ozmen L, Huang S, Gallay P, et al. Interferon gamma receptor deficient mice are resistant to endotoxic shock. The Journal of experimental medicine. 1994;179[5]:1437-44.

[144] Miles RH, Paxton TP, Dries DJ, Gamelli RL. Interferon-gamma increases mortality following cecal ligation and puncture. The Journal of trauma. 1994;36[5]:607-11.

[145] Dinges MM, Schlievert PM. Role of T cells and gamma interferon during induction of hypersensitivity to lipopolysaccharide by toxic shock syndrome toxin 1 in mice. Infection and immunity. 2001;69[3]:1256-64.

[146] Yin K, Gribbin E, Wang H. Interferon-γ inhibition attenuates lethality after cecal ligation and puncture in rats: implication of high mobility group box-1. Shock. 2005;24[4]:396-401.

[147] Nagarajan NA, Kronenberg M. Invariant NKT cells amplify the innate immune response to lipopolysaccharide. The Journal of Immunology. 2007;178[5]:2706-13.

[148] Etogo AO, Nunez J, Lin CY, Toliver-Kinsky TE, Sherwood ER. NK but not CD1-restricted NKT cells facilitate systemic inflammation during polymicrobial intra-abdominal sepsis. The Journal of Immunology. 2008;180[9]:6334-45.

[149] Döcke W-D, Randow F, Syrbe U, Krausch D, Asadullah K, Reinke P, et al. Monocyte deactivation in septic patients: restoration by IFN-γ treatment. Nature medicine. 1997;3[6]:678-81.

[150] Döcke W, Platzer C, Syrbe U, Meisel C, Zuckermann H, Klug C, et al. Monocytic deactivation in fatal septic disease: role of tumor necrosis factor-alpha and interleukin-10. MOF, MODS and SIRS Basic Mechanisms in Inflammation and Tissue Injury. 1996:162-8.

[151] Guo Y, Patil NK, Luan L, Bohannon JK, Sherwood ER. The biology of natural killer cells during sepsis. Immunology. 2018;153[2]:190-202.

[152] Menezes GB, Lee W-Y, Zhou H, Waterhouse CCM, Cara DC, Kubes P. Selective down-regulation of neutrophil Mac-1 in endotoxemic hepatic microcirculation via IL-10. The Journal of Immunology. 2009;183[11]:7557-68.

[153] van Roon J, Wijngaarden S, Lafeber FP, Damen C, van de Winkel J, Bijlsma JW. Interleukin 10 treatment of patients with rheumatoid arthritis enhances Fc gamma receptor expression on monocytes and responsiveness to immune complex stimulation. The Journal of rheumatology. 2003;30[4]:648-51.

[154] Kumar A, Zanotti S, Bunnell G, Habet K, Añel R, Neumann A, et al. Interleukin-10 blunts the human inflammatory response to lipopolysaccharide without affecting the cardiovascular response. Critical care medicine. 2005;33[2]:331-40.

[155] Ono S, Ueno C, Aosasa S, Tsujimoto H, Seki S, Mochizuki H. Severe sepsis induces deficient interferon-gamma and interleukin-12 production, but interleukin-12 therapy improves survival in peritonitis. The American journal of surgery. 2001;182[5]:491-7.

[156] Ono S, Tsujimoto H, Matsumoto A, Ikuta S-i, Kinoshita M, Mochizuki H. Modulation of human leukocyte antigen-DR on monocytes and CD16 on

granulocytes in patients with septic shock using hemoperfusion with polymyxin B-immobilized fiber. The American journal of surgery. 2004;188[2]:150-6.

[157] Gogos CA, Drosou E, Bassaris HP, Skoutelis A. Pro-versus anti-inflammatory cytokine profile in patients with severe sepsis: a marker for prognosis and future therapeutic options. The Journal of infectious diseases. 2000;181[1]:176-80.

[158] Frencken JF, van Vught LA, Peelen LM, Ong DS, Klein Klouwenberg P, Horn J, et al. An unbalanced inflammatory cytokine response is not associated with mortality following sepsis: a prospective cohort study. Critical care medicine. 2017;45[5]:e493-e9.

[159] Remick DG, Garg SJ, Newcomb DE, Wollenberg G, Huie TK, Bolgos GL. Exogenous interleukin-10 fails to decrease the mortality or morbidity of sepsis. Critical care medicine. 1998;26[5]:895-904.

[160] Steinhauser ML, Hogaboam CM, Kunkel SL, Lukacs NW, Strieter RM, Standiford TJ. IL-10 is a major mediator of sepsis-induced impairment in lung antibacterial host defense. The Journal of Immunology. 1999;162[1]:392-9.

[161] Kalechman Y, Gafter U, Gal R, Rushkin G, Yan D, Albeck M, et al. Anti-IL-10 therapeutic strategy using the immunomodulator AS101 in protecting mice from sepsis-induced death: dependence on timing of immunomodulating intervention. The Journal of Immunology. 2002;169[1]:384-92.

[162] Li X, Xu Z, Pang X, Huang Y, Yang B, Yang Y, et al. Interleukin-10/lymphocyte ratio predicts mortality in severe septic patients. PLoS One. 2017;12[6]:e0179050.

[163] Jensen IJ, McGonagill PW, Butler NS, Harty JT, Griffith TS, Badovinac VP. NK Cell–Derived IL-10 Supports Host Survival during Sepsis. The Journal of Immunology. 2021;206[6]:1171-80.

[164] Akhurst RJ, Hata A. Targeting the TGFβ signalling pathway in disease. Nature reviews Drug discovery. 2012;11[10]:790-811.

[165] Chantry D, Turner M, Abney E, Feldmann M. Modulation of cytokine production by transforming growth factor-beta. The Journal of Immunology. 1989;142[12]:4295-300.

[166] Espevik T, Figari IS, Shalaby MR, Lackides GA, Lewis GD, Shepard HM, et al. Inhibition of cytokine production by cyclosporin A and transforming growth factor beta. The Journal of experimental medicine. 1987;166[2]:571-6.

[167] Luan Y-y, Yin C-f, Qin Q-h, Dong N, Zhu X-m, Sheng Z-y, et al. Effect of regulatory T cells on promoting apoptosis of T lymphocyte and its regulatory mechanism in sepsis. Journal of Interferon & Cytokine Research. 2015;35[12]:969-80.

[168] Nullens S, De Man J, Bridts C, Ebo D, Francque S, De Winter B. Identifying therapeutic targets for sepsis research: A characterization study of the inflammatory players in the cecal ligation and puncture model. Mediators of inflammation. 2018;2018.

[169] Roquilly A, McWilliam HE, Jacqueline C, Tian Z, Cinotti R, Rimbert M, et al. Local modulation of antigen-presenting cell development after resolution of pneumonia induces long-term susceptibility to secondary infections. Immunity. 2017;47[1]:135-47. e5.

[170] Kay A, Barata L, Meng Q, Durham S, Ying S. Eosinophils and eosinophil-associated cytokines in allergic inflammation. International archives of allergy and immunology. 1997;113[1-3]:196-9.

[171] Hultgren O, Kopf M, Tarkowski A. Outcome of Staphylococcus aureus-triggered sepsis and arthritis in IL-4-deficient mice depends on the genetic background of the host. European journal of immunology. 1999;29[8]:2400-5.

[172] Burkovskiy I, Sardinha J, Zhou J, Lehmann C. Cytokine release in sepsis. Advances in bioscience and biotechnology. 2013;4[09]:860.

[173] Song GY, Chung C-S, Chaudry IH, Ayala A. IL-4–induced activation of the Stat6 pathway contributes to the suppression of cell-mediated immunity and death in sepsis. Surgery. 2000;128[2]:133-8.

[174] Surbatovic M, Filipovic N, Radakovic S, Stankovic N, Slavkovic Z. Immune cytokine response in combat casualties: blast or explosive trauma with or without secondary sepsis. Military medicine. 2007;172[2]:190-5.

[175] Tracey KJ, Cerami A. Tumor necrosis factor: an updated review of its biology. Critical care medicine. 1993;21[10 Suppl]:S415-22.

[176] Tracey KJ, Fong Y, Hesse DG, Manogue KR, Lee AT, Kuo GC, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature. 1987;330[6149]:662-4.

[177] Vacheron F, Mandine E, Lenaour R, Smets P, Zalisz R, Guenounou M. Inhibition of production of tumor necrosis factor by monoclonal antibodies to lipopolysaccharides. Journal of Infectious Diseases. 1992;165[5]:873-8.

[178] Borrelli E, Roux-Lombard P, Grau GE, Girardin E, Ricou B, Dayer J-M, et al. Plasma concentrations of cytokines, their soluble receptors, and antioxidant vitamins can predict the development of multiple organ failure in patients at risk. Critical care medicine. 1996;24[3]:392-7.

[179] Fisher Jr CJ, Agosti JM, Opal SM, Lowry SF, Balk RA, Sadoff JC, et al. Treatment of septic shock with the tumor necrosis factor receptor: Fc fusion protein. New England Journal of Medicine. 1996;334[26]:1697-702.

[180] Ali T, Sindhu Kaitha SM, Ftesi A, Stone J, Bronze MS. Clinical use of anti-TNF therapy and increased risk of infections. Drug, healthcare and patient safety. 2013;5:79.

[181] Opal SM, Fisher CJ, Dhainaut J-FA, Vincent J-L, Brase R, Lowry SF, et al. Confirmatory interleukin-1 receptor antagonist trial in severe sepsis: a phase III, randomized, doubleblind, placebo-controlled, multicenter trial. Critical care medicine. 1997;25[7]:1115-24.

[182] Flierl MA, Rittirsch D, Gao H, Hoesel LM, Nadeau BA, Day DE, et al. Adverse functions of IL-17A in experimental sepsis. The FASEB Journal. 2008;22[7]:2198-205.

[183] Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, et al. Cytokine profiles as markers of disease severity in sepsis: a multiplex analysis. Critical care. 2007;11[2]:R49.

[184] Rau M, Schiller M, Krienke S, Heyder P, Lorenz H, Blank N. Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis. The Journal of rheumatology. 2010;37[11]:2369-76.

[185] Tschoeke SK, Oberholzer A, Moldawer LL. Interleukin-18: a novel prognostic cytokine in bacteria-induced sepsis. Critical care medicine. 2006;34[4]:1225-33.

[186] Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. American journal of respiratory and critical care medicine. 2012;185[11]:1225-34.

[187] Monneret G, Lepape A, Voirin N, Bohé J, Venet F, Debard A-L, et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock. Intensive care medicine. 2006;32[8]:1175-83.

[188] Monneret G, Debard A-L, Venet F, Bohe J, Hequet O, Bienvenu J, et al. Marked elevation of human circulating CD4+ CD25+ regulatory T cells in sepsis-induced immunoparalysis. Critical care medicine. 2003;31[7]:2068-71.

[189] Flohé S, Börgermann J, Dominguez FE, Majetschak M, Lim L, Kreuzfelder E, et al. Influence of granulocyte-macrophage colony-stimulating factor [GM-CSF] on whole blood endotoxin responsiveness following trauma, cardiopulmonary bypass, and severe sepsis. Shock [Augusta, Ga]. 1999;12[1]:17-24.

[190] Rosenbloom AJ, Linden PK, Dorrance A, Penkosky N, Cohen-Melamed MH, Pinsky MR. Effect of granulocyte-monocyte colony-stimulating factor therapy on leukocyte function and clearance of serious infection in nonneutropenic patients. Chest. 2005;127[6]:2139-50.

[191] Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, et al. Granulocyte–macrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. American journal of respiratory and critical care medicine. 2009;180[7]:640-8.

[192] Venet F, Foray A-P, Villars-Méchin A, Malcus C, Poitevin-Later F, Lepape A, et al. IL-7 restores lymphocyte functions in septic patients. The Journal of immunology. 2012;189[10]:5073-81.

[193] Shindo Y, Fuchs AG, Davis CG, Eitas T, Unsinger J, Burnham CAD, et al. Interleukin 7 immunotherapy improves host immunity and survival in a two-hit model of Pseudomonas aeruginosa pneumonia. Journal of leukocyte biology. 2017;101[2]:543-54.

[194] Francois B, Jeannet R, Daix T, Walton AH, Shotwell MS, Unsinger J, et al. Interleukin-7 restores lymphocytes in septic shock: the IRIS-7 randomized clinical trial. JCI insight. 2018;3[5].

[195] Kimura A, Ono S, Hiraki S, Takahata R, Tsujimoto H, Miyazaki H, et al. The postoperative serum interleukin-15 concentration correlates with organ dysfunction and the prognosis of septic patients following emergency gastrointestinal surgery. Journal of Surgical Research. 2012;175[2]:e83-e8.

[196] Zhao X, Qi H, Zhou J, Xu S, Gao Y. Treatment with Recombinant Interleukin-15 [IL-15] Increases the Number of T Cells and Natural Killer [NK] Cells and Levels of Interferon-γ [IFN-γ] in a Rat Model of Sepsis. Medical science monitor: international medical journal of experimental and clinical research. 2019;25:4450.

[197] Velavan TP, Meyer CG. The COVID-19 epidemic. Tropical medicine & international health. 2020;25[3]:278.

[198] Li H, Liu L, Zhang D, Xu J, Dai H, Tang N, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. The Lancet. 2020;395[10235]:1517-20.

[199] Hu B, Huang S, Yin L. The cytokine storm and COVID-19. Journal of medical virology. 2021;93[1]:250-6.

[200] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The lancet. 2020;395[10223]:497-506.

[201] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The lancet. 2020;395[10229]:1033-4.

[202] Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. The Lancet Rheumatology. 2020;2[6]:e325-e31.

[203] Capra R, De Rossi N, Mattioli F, Romanelli G, Scarpazza C, Sormani MP, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. European journal of internal medicine. 2020;76:31-5.

[204] McElvaney OJ, Curley GF, Rose-John S, McElvaney NG. Interleukin-6: obstacles to targeting a complex cytokine in critical illness. The Lancet Respiratory Medicine. 2021.

[205] Dheir H, Yaylaci S, Sipahi S, Genc AC, Cekic D, Tuncer FB, et al. Does Macrophage Migration Inhibitory Factor predict the prognosis of COVID-19 disease? The Journal of Infection in Developing Countries. 2021;15[03]:398-403.

[206] Bleilevens C, Soppert J, Hoffmann A, Breuer T, Bernhagen J, Martin L, et al. Macrophage Migration Inhibitory Factor [MIF] Plasma Concentration in Critically Ill COVID-19 Patients: A Prospective Observational Study. Diagnostics. 2021;11[2]:332.