in vivo *27*: 669-684 (2013)

Review

Role of Cytokines as a Double-edged Sword in Sepsis

HINA CHAUDHRY[1], JUHUA ZHOU[2,3], YIN ZHONG[2], MIR MUSTAFA ALI[1], FRANKLIN MCGUIRE[1], PRAKASH S. NAGARKATTI[2] and MITZI NAGARKATTI[2]

[1]Division of Pulmonary and Critical Care Medicine, and [2]Department of Pathology, Microbiology, and Immunology, University of South Carolina School of Medicine, Columbia, SC, U.S.A.; [3]Institute for Tumor Immunology, Ludong University School of Life Sciences, Yantai, Shandong, P.R. China

Abstract. *Background: Sepsis is a deadly immunological disorder and its pathophysiology is still poorly understood. We aimed to determine if specific pro-inflammatory and anti-inflammatory cytokines can be used as diagnostic and therapeutic targets for sepsis. Materials and Methods: Recent publications in the MEDLINE database were searched for articles regarding the clinical significance of inflammatory cytokines in sepsis. Results: In response to pathogen infection, pro-inflammatory cytokines [interleukin-6 (IL-6), IL-8, IL-18 and tumor necrosis factor-α (TNF-α)] and anti-inflammatory cytokine (IL-10) increased in patients with sepsis. Importantly, a decrease in IL-6 was associated with a better prognosis and overproduction of IL-10 was found to be the main predictor of severity and fatal outcome. Conclusion: Both pro-inflammatory and anti-inflammatory cytokines constitute a double-edged sword in sepsis; on one hand they are critical to eliminate the infection while on the other, excessive production can cause tissue and organ damage. Increase in cytokines such as IL-6, Il-8, IL-10, IL-18 and TNF-α may have implications in diagnosis and treatment of sepsis.*

Sepsis and sepsis-associated multi-organ failure are a tremendous burden for healthcare systems and constitute a major challenge to scientists. Despite extensive basic research and clinical studies, the pathophysiology of sepsis is still poorly understood. It is increasingly becoming clear that sepsis is a heterogeneous and dynamic disorder, which results from imbalances in the inflammatory network (1). Sepsis is exhibited as a whole-body or a systemic inflammatory response syndrome (SIRS), in the presence of a known or suspected infection. It becomes severe following organ dysfunction, which results from low blood pressure, or insufficient blood flow to one or more organs due to lactic acidosis, reduced urine production and altered mental status. Severe sepsis is defined as sepsis with organ dysfunction including hypotension (<90 mmHg or a reduction of ≥40 mmHg from baseline), hypoxemia, oliguria, metabolic acidosis, thrombocytopenia and obtundation (2). Sepsis can also cause septic shock, multiple organ dysfunction syndrome and death. Septic shock is defined as severe sepsis with at least any two SIRS criteria, including tachypnea, white blood cell count abnormality, high heart rate and fever or hypothermia, and presumed infection in which the patient remains hypotensive despite adequate fluid challenge. Septic shock and multi-organ dysfunction are the most common causes of death in patients with sepsis (3).

The worldwide yearly mortality from sepsis is considerable, and it is greater than that from both lung and breast cancer. Furthermore, the incidence of sepsis is increasing, however, currently there is no effective treatment available for sepsis (4). There are about 750,000 cases of sepsis annually in the United States. Overall, sepsis is the second-leading cause of death in the United States in patients in non-coronary intensive care units (ICUs) and the tenth most common cause of death according to data reported from the Centers for Disease Control and Prevention (5). In the United States, sepsis is also the leading cause of death in critically ill patients and more than 210,000 sepsis patients die each year (6). Sepsis is common and also more dangerous in elderly, immunocompromised and critically ill patients. It accounts for 1-2% of all hospitalizations and occurs in ~25% of ICU bed utilization. It is a main cause of death in ICUs worldwide, for instance, the mortality rates are 20% for sepsis, 40% for severe sepsis and >60% for septic shock (7, 8).

Correspondence to: Dr. Juhua Zhou, Institute for Tumor Immunology, Ludong University School of Life Sciences, 186 Hongqi Middle Road, Yantai, Shandong 264025, PR China. Tel: +1 86 1830 050 1903, Fax: +1 86 0535 664 2910, e-mail: Juhua.Zhou@gmail.com

Key Words: Sepsis, cytokine, pro-inflammatory, anti-inflammatory, biomarker, signaling pathway, review.

Sepsis results from the complicated interactions between the infecting bacteria or viruses and the host immune system. A high burden of infection, the presence of superantigens and other virulence factors, resistance to opsonization and phagocytosis, and antibiotic resistance lead to sepsis progression when the host cannot inhibit the infection (9). Such infections also trigger a cytokine storm, which is often detected in patients with sepsis. In this review, the production, functions and underlying mechanisms of cytokines in response to infection in patients with sepsis are discussed. Results from cytokine research also have great implications in the prevention and treatment of sepsis.

Pro-inflammatory Cytokines in Sepsis

Cytokines are regulators of the immune response to infection and play a key role in regulating inflammation and trauma. There are two types of cytokines. Pro-inflammatory cytokines stimulate systematic inflammation, whereas anti-inflammatory cytokines inhibit inflammation and enhance healing. The major pro-inflammatory cytokines that regulate early responses include interleukin-1α (IL-1α), IL-1β, IL-6, and tumor necrosis factor-α (TNF-α). Other pro-inflammatory mediators include members of the IL-20 family, leukemia inhibitory factor (LIF), interferon-γ (IFN-γ), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), transforming growth factor-β (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8, IL-11, IL-12, IL-17, IL-18, IL-33 and a variety of other chemokines that attract inflammatory cells. Pro-inflammatory cytokines act as endogenous pyrogens (IL-1, IL-6, TNF-α), up-regulate the synthesis of secondary mediators and other pro-inflammatory cytokines by both macrophages and mesenchymal cells, such as fibroblasts, epithelial and endothelial cells, and stimulate the production of acute phase proteins, or attract inflammatory cells. Host immunosuppression may be responsible for late death in patients with sepsis (10, 11). It has been reported that immunosuppression results from the apoptosis of circulating and tissue lymphocytes such as B-cells and $CD4^+$ T-cells and dendritic cells (DCs) (12). Below, we discuss the individual role played by the different cytokines involved in sepsis.

IL-1β. Also known as catabolin, IL-1β is a member of the interleukin-1 cytokine family. This cytokine is produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase-1. IL-1β is an important mediator of the inflammatory response, and is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. The role of IL-1β in sepsis has not been extensively studied. It has been reported that after simultaneous measurement of 17 cytokines during the first seven days after admission of patients with sepsis, IL-1β exhibited persistent increases in those who died (13), suggesting that IL-1β may play a role in sepsis.

IL-6. Also called interferon-β2 and B-cell stimulatory factor-2 (BSF-2), IL-6 is a pleiotropic interleukin, and interestingly, functions as both a pro-inflammatory and anti-inflammatory cytokine. The IL-6 family of cytokines also includes IL-11, oncostatin M, leukemia inhibitory factor, ciliary neurotrophic factor, cardiotrophin-1, and cardiotrophin-like cytokine. All cytokines of the IL-6 family use the glycoprotein 130 (Gp130) (also known as IL-6Rß or CD130) receptor as a signaling subunit (14). IL-6 is secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation. IL-6 can also be secreted by macrophages in response to specific microbial molecules, referred to as pathogen associated molecular patterns (PAMPs). These PAMPs bind to a highly important group of detection molecules of the innate immune system, called pattern recognition receptors (PRRs), including toll-like receptors (TLRs). They are present on the cell surface and intracellular compartments and induce intracellular signaling cascades, leading to inflammatory cytokine production. Thus, IL-6 is relevant to many disease processes such as cancer (15), cardiovascular disease (16), and autoimmune diseases (17). Such findings suggest that IL-6 may also play a role in sepsis.

It has been documented that IL-6 production is elevated in patients with sepsis (13, 18), indicating that IL-6 is associated with the development of sepsis (18). Further studies indicated that the IL-6 level in patients with shock is higher than that in patients without shock, and in those who died from severe sepsis (19), suggesting that IL-6 is the key cytokine in the pathophysiology of severe sepsis. In addition, an increased level of IL-6 was found to be associated with the highest risk of death in patients with sepsis (20). Among the milieu of cytokines induced during sepsis, plasma IL-6 has the best correlation with mortality rate (21). The precise mechanisms through which IL-6 regulates sepsis are not clear and additional research is needed.

IL-8. IL-8 is a chemokine produced by macrophages and other cell types, including epithelial cells and endothelial cells. IL-8 belongs to the Cysteine X Cysteine (CXC) family of chemokines. The CXC nomenclature relates to the presence of two conserved cysteine residues at the amino terminus separated by one amino acid. IL-8 belongs to a subdivision of CXC chemokines which has the amino acid sequence Glu-Leu-Arg (ELR) preceding the first conserved cysteine amino acid residue in its primary structure. CXC chemokines with the ELR motif are potent angiogenic factors (22).

IL-8 is one of the major mediators of the inflammatory response. Its primary function is the induction of chemotaxis in its target cells, *e.g.* neutrophil granulocytes. IL-8 serves as a chemical signal that attracts neutrophils to the site of inflammation, and therefore is also known as neutrophil chemotactic factor. IL-8 has implications in human disease, such as periodontitis (23) and psoriasis (24).

It has been reported that serum and plasma levels of IL-8 were enhanced in patients with sepsis (25). Further investigations suggest that the initial levels of IL-8 were the most predictive factor for death in patients with sepsis (13), indicating that IL-8 may play a role in sepsis.

IL-12. IL-12 is a cytokine that is naturally produced by dendritic cells, macrophages and B-lymphoblastoid cells in response to antigenic stimulation. IL-12 is involved in the differentiation of naïve T-cells into T helper type 1 (Th1) cells (26). It stimulates the production of IFN-γ and TNF-α from T- and natural killer (NK) cells, and reduces IL-4-mediated suppression of IFN-γ. IL-12 has been shown to be important in both infectious and autoimmune disease (27). Serum cytokine levels of IL-12 were increased in patients with sepsis (13), thereby suggesting its role in sepsis.

IL-17. IL-17 is the founding member of the IL-17 family. It functions as a pro-inflammatory cytokine. When the immune system responds to the invasion of extracellular pathogens, IL-17 is involved in excessive tissue damage (28). IL-17 also is a potent mediator in the regulation of hemopoiesis and inflammation by increasing chemokine production in various tissues to recruit monocytes (29) and neutrophils (30) to the site of inflammation. IL-17 is produced by helper T-cells and is induced by IL-23, which results in destructive tissue damage in chronic inflammatory diseases (31).

IL-17 stimulates the production of many other cytokines including IL-6, granulocyte-colony stimulating factor (G-CSF), GM-CSF, IL-1β, TGF-β, TNF-α, chemokines [including IL-8, growth-related oncogene-α (GRO-α), and monocyte chemotactic protein-1 (MCP-1)] and prostaglandins (PGE2) from many cell types such as fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages (32). The release of these cytokines has many consequences such as airway remodeling (33), a characteristic of response to IL-17. Thus, IL-17 is commonly associated with allergic responses (34). IL-17 also plays a key role in the functioning of a subset of $CD4^+$ T-cells, called Th17 cells (35). Th17 cells play an important role in many immune/autoimmune-related diseases such as rheumatoid arthritis, asthma, lupus, allograft rejection and antitumor immunity (36).

The role of IL-17 in sepsis is controversial. Several studies suggested that IL-17 is crucial for the protection against *Candida* infection, whereas other studies reported that IL-17 may contribute to inflammatory pathology and worsening of fungal disease. IL-17 was shown not have a major contribution to the inflammatory pathology leading to organ failure in fungal sepsis, suggesting that the IL-17 pathway is rather protective in antifungal host defense (37). It has been also reported that IL-17 may take part in host protection during polymicrobial sepsis (38). A multiplex analysis in 60 patients with severe sepsis showed that IL-17 was undetectable (39).

IL-18. Formerly named IFN-γ-inducing factor, IL-18 belongs to the IL-1 superfamily. IL-18 is a pro-inflammatory Th1 cytokine. Macrophages and other cells produce IL-18 (40). IL-18 may stimulate NK cells and certain T-cells to release IFN-γ or type II interferon, which plays an important role in activating the macrophages or other cells. IL-18 can induce cell-mediated immunity in response to infection with microbial products such as lipopolysaccharide (LPS).

IL-18 has been suggested to play a significant role in the pathophysiology of sepsis. Serum cytokine levels of IL-18 were elevated in patients with sepsis (41). Studies have shown that elevated plasma IL-18 concentrations are associated with poor clinical outcome in severe inflammatory and septic conditions. Moreover, a significant increase in IL-18 concentrations may be used in the discrimination between Gram-positive- and Gram-negative-related sepsis (42).

IFN-γ. Also known as type II interferon, IFN-γ is a cytokine that is critical for innate and adaptive immunity against viral and intracellular bacterial infections and for tumor control (43). CD4 and CD8 T-cells predominantly produce IFN-γ upon antigen stimulation, and NK cells also produce IFN-γ in the innate immune response. IFN-γ is the primary cytokine used to define Th1 cells. Abnormal expression of IFN-γ has been shown to be related to a number of inflammatory and autoimmune diseases (43).

It has been reported that homozygotes for the D allele of the IFN-γ gene have an increased risk for developing sepsis after traumatic injury compared with those with other allelic combinations (44), suggesting that IFN-γ may play a role in sepsis. Several studies indicated that IFN-γ promoted the pro-inflammatory response during septic shock (45). IFN-γ expression was enhanced persistently in patients who died of sepsis (13), however, treatment of IFN-γ neutralization did not improve survival consistently (45). Furthermore, survival after sepsis was associated with the improvement of the pro-inflammatory, but not the anti-inflammatory response (46). Severe sepsis led to deficient IFN-γ production, and there was an elevation of Th2 cytokine and a decrease in Th1 cytokine in the patients with severe sepsis (47). Nevertheless, IFN-γ is a potent agent for the treatment of hemorrhagic shock-induced

immunosuppression. It may increase the ability of the host immune system to inhibit bacterial infections. Thus, IFN-γ decreased the susceptibility to sepsis after hemorrhage (48). Taken together, such studies stress the need to pursue further research on the role of IFN-γ in sepsis.

GM-CSF. This is a cytokine which stimulates white blood cell growth. It is secreted by macrophages, T-cells, mast cells, endothelial cells, and fibroblasts. GM-CSF induces stem cells to develop into neutrophils, eosinophils, basophils and monocytes (49). GM-CSF may also have a pro-inflammatory function (50). The role of GM-CSF in sepsis has not been well-elucidated.

It has been reported that GM-CSF increased persistently in patients who died of sepsis (13). However, a multiplex analysis in 60 patients with severe sepsis showed that GM-CSF was not detectable (39). An *in vitro* culture study suggested that GM-CSF increases immune functions in severely injured patients vulnerable to bacterial sepsis (51). Considering immunosuppression in sepsis, GM-CSF has been used in a clinical trial for the treatment of patients with sepsis (52). However, a recent meta-analysis suggested there was not enough data to support the routine use of GM-CSF in patients with sepsis (53).

TNF-α. Stimulating the acute phase reaction involved in systemic inflammation, TNF-α has also been shown to induce apoptotic cell death, and inhibit tumorigenesis and viral replication (54, 55). Dysregulation of TNF-α production has been implicated in a variety of human diseases, including major depression (56), Alzheimer's disease (57) and cancer (58). It has been documented that the plasma levels of TNF-α increased significantly in patients with sepsis and in animal models (13). TNF-α has become the pro-inflammatory cytokine most well-studied in sepsis.

Other cytokines. High-mobility group box-1 (HMGB1), a highly conserved protein, is also known as a DNA-binding protein. It is involved in the maintenance of nucleosome structure and regulation of gene transcription. HMGB1 was also recently found to function as a potent pro-inflammatory cytokine in response to infection. Levels of HMGB1 were found to be enhanced in serum and tissues during infection, especially in sepsis (59). In another study, after measurement of 17 cytokines in 30 patients with sepsis, a significant positive association was noted between the levels of MCP-1 and macrophage inflammatory protein (MIP)-1β in the first three days and the scores of sepsis-related organ failure assessment on day 1 (13). Thus, in addition to the well-established cytokines, there may be others which may play a role in the regulation of pathogenesis of sepsis (60).

Anti-inflammatory Cytokines in Sepsis

The anti-inflammatory cytokines are a group of immunoregulatory molecules that are involved in the prevention of potentially harmful effects of persistent or excess inflammatory reactions. Major anti-inflammatory cytokines include IL-1 receptor antagonist (IL-1Ra), IL-4, IL-6, IL-10, IL-11, and IL-13 (61). Anti-inflammatory cytokines may also play a role in sepsis.

IL-1Ra. A 152-amino-acid protein, it acts as a specific inhibitor for the two other functional members of the IL-1 family, IL-1α and IL-1β. IL-1Ra competes with IL-1α and IL-1β in the binding to IL-1 receptor and thus blocks the function of IL-1α and IL-1β. IL-1Ra binding to IL-1 receptor prevents cellular activation by IL-1α or IL-1β by steric inhibition (62). Some anti-inflammatory cytokines, including IL-4, IL-6, IL-10, and IL-13, increase the synthesis of IL-1Ra but also inhibit the synthesis of IL-1β (63).

In a rat model of sepsis induced by cecal ligation and puncture (CLP), IL-1Ra treatment inhibited the acute hemodynamic, hypothermic, and fatal effects of Gram-negative sepsis (64). The results indicated that IL-1 receptor blockade may be an important novel treatment strategy against overwhelming bacterial sepsis. Nevertheless, the role of IL-1Ra in patients with sepsis is still unclear.

IL-4. A pleiotropic cytokine, IL-4 was initially identified as a B-cell differentiation factor, as well as a B-cell stimulatory factor. It is produced by activated T-cells, mast cells and basophils. IL-4 has many biological roles. It can stimulate the proliferation of activated B-cells and T-cells, and induce the differentiation of $CD4^+$ T-cells into Th2 cells. Excessive production of IL-4 is associated with allergies (65). In animals with sepsis, IL-4 induces the activation of the Stat6 pathway, suppressing cell-mediated immunity and death (66). However, enzyme-linked immunosorbent assays (ELISA) in 56 cases with severe trauma who developed sepsis, of whom 36 died, indicated that IL-4 had no significant correlation with the severity and outcome of sepsis (67). Moreover, studies on the disruption of the IL-4 gene in two inbred mouse strains demonstrated different roles of IL-4 in *Staphylococcus aureus*-induced sepsis. In 129SV mice, IL-4 was beneficial; however, in C57BL/6 mice, IL-4 was unfavorable (68). Thus, the precise role of IL-4 in sepsis is not clear.

IL-10. IL-10 is the key cytokine in anti-inflammatory responses. $CD4^+$ Th2 cells, monocytes and B-cells produce IL-10. IL-10 powerfully inhibits the expression of Th1 cytokines, including both IL-2 and IFN-γ. After binding to its high-affinity IL-10 receptor, IL-10 also suppresses the production of TNF-α, IL-1, IL-6, IL-8, IL-12, GM-CSF, MIP-1α and MIP-2α in monocytes, macrophages, neutrophils and NK cells (61).

It has been reported that IL-10 is one of the critical cytokines in the pathophysiology of sepsis (19). Measurement of serum cytokines in patients with severe sepsis indicated that the IL-10 level was significantly enhanced (41, 67). Increased IL-10 levels in serum were correlated with the sepsis score and death. A high IL-10-to-TNF-α ratio was associated with death. Furthermore, persistent overproduction of IL-10 is the main risk factor for sepsis severity and fatal outcome (69), suggesting that patients with sepsis are in profound immunosuppression.

IL-11. IL-11 is a member of the Gp130 family of cytokines. IL-11 has hematopoietic, immunomodulatory and epithelial cell-protective activities. IL-11 is usually not detected in the systemic circulation; however, it may be detected in localized areas of inflammation. IL-11 binds to its own unique receptor, IL-11α, and then activates Gp130, like IL-6 (70). IL-11 has been shown to act as a Th2-type cytokine. It induces the expression of IL-4, but inhibits the production of IFN-γ and IL-2, the Th1-type cytokines (71). Reverse transcription-polymerase chain reaction (RT-PCR) analysis demonstrated a considerable increase in *IL-11* mRNA level in the femurs of group B *Streptococcus* (GBS)-infected neonatal rats with sepsis. Prophylactic administration of IL-11 was potentially effective in the treatment of GBS sepsis in neonatal rats (72). Oral administration of IL-11 also inhibited infection in a neutropenic rat model of Gram-negative sepsis (73). However, the role of IL-11 in patients with sepsis is still unclear.

IL-13. IL-13 is an important cytokine in allergic inflammation and disease. Many cell types, especially Th2 cells, secret IL-13 (74). IL-13 and IL-4 have a common cellular receptor, IL-4 type 1 receptor. Thus, IL-13 and IL-4 have many similarities in anti-inflammatory responses (75). IL-13 reduces the expression of TNF-α, IL-1, IL-8, and MIP-1α in monocytes (76). IL-13 also inhibits the production of TNF-α, IFN-γ and IL-12 and thus improves LPS-induced lethality in animal models (77), suggesting that IL-13 may play a role in sepsis.

It has been reported that the intestinal concentration of IL-13 was dramatically increased in rats with sepsis as compared with healthy normal rats (78). However, IL-13 was not detected in plasma in patients with sepsis and increased IL-13 production was not found to take part in an inducible host defense mechanism during sepsis (79). Further studies will be necessary to elucidate the role of IL-13 in sepsis.

IL-35. A recently-discovered anti-inflammatory cytokine belonging to the IL-12 family (80), IL-35 is a heterodimeric cytokine composed of IL-12α and IL-27β chains. Regulatory T-cells produce IL-35, but effector T-cells do not (80). IL-35 converts naive T-cells into IL-35-producing induced regulatory T-cells, stimulates regulatory T-cell proliferation and is required for the maximal suppressive function of regulatory T-cells (81, 82). It has been reported that IL-35 reduces Th17 cell activity (82) and suppresses inflammation in inflammatory bowel disease (80). IL-35 may contribute to infectious tolerance (83), suggesting that IL-35 may play a role in immunosuppression in sepsis. The role of IL-35 in sepsis, however, has not been studied thus far.

TGF-β. An anti-inflammatory cytokine, TGF-β is involved in the control of cell proliferation, cell differentiation, and other functions in many cells. For instance, TGF-β suppresses the proliferation and differentiation of T- and B-cells. It may also antagonize or modify the functions of other cytokines or growth factors. For example, TGF-β inhibits the production of IL-2, IFN-γ and TNF. As an anti-inflammatory cytokine, TGF-β is an important regulator of the immune system by regulatory T-cells. TGF-β also inhibits the activation of lymphocytes and monocyte-derived phagocytes. TGF-β1 suppresses the functions of monocytes and macrophages in a manner similar to IL-10. However, TGF-β is less potent than IL-10 and has little or no effect on IL-1 production.

TGF-β was elevated in the blood from mice with sepsis (84) and increased in the circulation and in adherent splenic cells in rats with sepsis (85). However, real-time PCR analysis in total RNA from foal blood samples indicated that expression of TGF-β was significantly decreased in the sick non-septic and septic groups, compared with the healthy group (86). After comparison of 28 patients with Gram-positive sepsis to 11 patients with Gram-negative sepsis and 15 healthy volunteers, it was found that there was no role for TGF-β in the development of Gram-positive sepsis nor in prognosis (87). These results suggest that TGF-β may not have a role in sepsis.

As stated above, both pro-inflammatory and anti-inflammatory cytokines may play critical roles in sepsis. Importantly, plasma and/or serum levels of IL-6, IL-8, IL10, IL-18 and TNF-α significantly increased in patients with sepsis. Enhanced production of IL-6, IL-8, IL-18 and TNF-α may be responsible for an excessive inflammatory state, whereas IL-10 may play a role in late immunosuppression in sepsis. Therefore, these cytokines are associated with disease severity and mortality in sepsis (Table I). Accordingly, transcription factors in the regulation of cytokine production may also play a role in sepsis. It was not surprising that activity of transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) was strongly correlated with the severity of sepsis and significantly associated with a higher rate of mortality (88, 89).

Cytokine Profile in Sepsis

Understanding the cytokine profile in patients with sepsis may be very useful in the diagnosis of disease severity, and prediction of mortality and better patient management.

Table I. *Role of major pro-inflammatory and anti-inflammatory cytokines in sepsis.*

Cytokine	Family	Cell origin	Function	Role in sepsis
Pro-inflammatory				
IL-1β	IL-1	Macrophages, monocytes	Cell proliferation, differentiation, apoptosis	Unknown
IL-6	IL-6	T-cells, macrophages, endothelial cells	Cell growth, differentiation, cytokine production	Disease severity, mortality, biomarker
IL-8	CXC	Macrophages, epithelial cells, endothelial cells	Chemotaxis, angiogenesis	Mortality, biomarker
IL-12	IL-12	Dendritic cells, macrophages, B-cells	IFN-γ production, TNF-α production, Th1 differentiation	Unknown
IL-17	IL-17	Helper T-cells	Cytokine/chemokine production, anti-tumor immunity, autoimmunity	Controversial
IL-18	IL-1	Macrophages, monocytes, dendritic cells	IFN-γ production, anti-microbial immunity	Disease severity, biomarker
IFN-γ	IFN	T-Cells, NK cells, NKT cells	Anti-infection, anti-tumor immunity, autoimmunity	Unclear
GM-CSF	IL-4	T-Cells, macrophages, mast cells, endothelial cells, fibroblasts	Cell growth, survival, granulocyte development, monocyte development, autoimmunity	Unclear
TNF-α	TNF	Macrophage, CD4 T-cells, NK cells	Cytokine production, cell proliferation, apoptosis, anti-infection, tumor necrosis	Disease progress, survival, biomarker
Anti-inflammatory				
IL-1Ra	IL-1	Macrophages, monocytes, dendritic cells	IL-1α inhibitor, IL-1β inhibitor	Unknown
IL-4	IL-4	T-Cells, mast cells, basophils	Cell proliferation, Th2 differentiation	Unclear
IL-10	IL-10	Th2 cells, B-cells, monocytes	Potent inhibitor of pro-inflammatory cytokine production	Disease severity, mortality
IL-11	IL-6	Fibroblasts, neurons, epithelial cells	Induction of Th2 cytokines, inhibition of Th1 cytokine production	Unknown
IL-13	IL-4	Th2 Cells	Inhibitor of pro-inflammatory cytokine production	Unknown
TGF-β	TGF-β	Macrophages, T-cells	Proliferation, apoptosis, differentiation, migration, inhibition of pro-inflammatory cytokine production	Unclear

IL: Interleukin; CD: cluster of differentiation; Th: T helper; IFN: interferon; TNF: tumor necrosis factor; TGF: transforming growth factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; CXC: cysteine X cysteine.

Cytokine assay by multiplex array in burnt mice with susceptibility to sepsis showed that IL-1β, IL-6, IL-17, G-CSF, GM-CSF, MIP-1α, RANTES (regulated on activation, normal T-cell expressed and secreted) and TNF-α were increased, but IL-2, IL-3 and IL-5 were decreased and IL-10, IFN-γ and IL-12p70 were expressed in a biphasic manner following the burn injury (90). There was a similar cytokine profile in mice and children after a severe burn (90), suggesting the utility of the burnt mouse model for development of therapeutic interventions to attenuate the post-burn inflammatory response. A multiplex analysis evaluating plasma levels of 17 cytokines in patients with severe sepsis discovered that the concentrations of IL-1β, IL-6, IL-7, IL-8, IL-10, IL-13, IFN-γ, MCP-1 and TNF-α were significantly higher in patients with septic shock than in those with severe sepsis, and distinct cytokine profiles were associated with severity of sepsis, evolution of organ failure and death (39).

Serial estimation of IL-6 and TNF-α in patients with sepsis on days 1, 3 and 7 after admission showed that IL-6 levels were reduced from day 1 to 7 in the survivor group and the TNF-α level was significantly low on day 1 in the non-survivor female group (21). These results suggest that a decreasing trend in IL-6 values was associated with a better prognosis in sepsis.

It has been reported that IL-10 paralleled the sepsis score and elevated serum IL-10 and TNF-α levels and a high IL-10 to TNF-α ratio were associated with death (69). The results demonstrate that the sustained overproduction of the anti-inflammatory cytokine IL-10 is the main predictor of severity and fatal outcome.

It has become clear that sepsis is typically characterized by an initial intense inflammatory response or cytokine storm (11). These cytokines trigger a beneficial inflammatory response, such as increased local coagulation and restricted tissue damage. Overwhelming production of these pro-

inflammatory cytokines, however, can be very dangerous in that excessive cytokines destroy the normal regulation of the immune response and induce pathological inflammatory disorders, such as capillary leakage, tissue injury and lethal organ failure (91).

The initial hyperinflammatory phase may be followed by immunosuppression in late sepsis (11). This theory is very important because it might help to explain these recent therapeutic failures and could innovate the way that new sepsis therapies are designed.

Cytokines in Neonatal Patients with Sepsis

Similar to adult patients, serum levels of IL-6, IL-8, IL-10, GM-CSF, IFN-γ, TNF-α and IL-12 significantly increased in neonatal patients who developed and died of sepsis (92). Furthermore, there was a positive correlation between serum TNF-α and IL-10 levels measured early in the course of sepsis and those detected in cord blood (93). It has been reported that enteral feeding with cow milk formula may induce sepsis. IFN-γ, IL-4, IL-10 and TGF-β1 were dramatically augmented in such neonatal patients (94). Such findings suggest that similar cytokines mechanisms may operate in sepsis in neonatal and adult patients.

Cytokines in Elderly Patients with Sepsis

There are very limited data available on elderly patients regarding cytokines in sepsis. Age-dependent defects in T- and B-cell function have been demonstrated in elderly patients (95). Thus, elderly patients have a considerable decrease in both cell-mediated immune function and reduced humoral immune function. Immune dysfunctions may contribute to enhanced susceptibility of elderly patients to sepsis. The cytokine and chemokine signaling networks may also be severely altered in elderly patients. For instance, a type 2 cytokine response is favored over type 1 cytokine responses in elderly adults (96). Immune dysfunctions may contribute to the enhanced susceptibility of elderly patients to sepsis.

Studies in mouse models of intra-abdominal sepsis indicated that aged mice displayed a significantly higher mortality rate and profound hypothermia. IL-1β, IL-6 and IL-10 were higher in the circulating blood with aging. In the heart and lungs, the expression of IL-6 and IL-10 mRNA was also significantly increased with aging. These results demonstrate an age-associated enhancement in mortality, hypothermia and induction of IL-6 during sepsis in mice (97). Serial estimation of IL-6 and TNF-α in elderly patients with sepsis indicated that IL-6 levels reduced in the survivor group from day 1 to 7, whereas the TNF-α level significantly decreased in the non-survivor group on day 1 (21). Further investigation will be needed in understanding the function of cytokines in elderly patients with sepsis.

Cytokines as a Biomarker in Sepsis

A reliable biomarker for the diagnosis and prognosis of sepsis is critical. The ideal biomarker for sepsis should be easy to determine analytically, highly specific and very sensitive, and assays should be inexpensive and readily available. Using such biomarkers would not only provide early diagnostic accuracy and prognostic information on sepsis but also predict the responsiveness to treatment interventions. Thus far, there are no such biomarkers available for sepsis. It is also impossible to develop such an ideal assay for sepsis diagnosis in the near future (98).

Although there are not ideal biomarkers available for sepsis, a number of existing and candidate biomarkers have been tested and may provide useful information to the clinicians caring for patients with sepsis (Table I) (98). It has been reported that there is an association of cytokine concentrations with the severity and evolution of organ dysfunction in patients with sepsis (39). Several studies have shown that high plasma levels of IL-18 correlated with poor clinical outcome in patients with sepsis (42), and thus IL-18 may constitute a candidate biomarker for sepsis.

Midkine, also known as neurite growth-promoting factor-2 (NEGF2), is a multifunctional cytokine. Recent studies indicate that midkine significantly increased in the patients with severe sepsis and septic shock (99). Sepsis-related global hypoxia may contribute to midkine enhancement. Midkine may have an application as a sepsis biomarker. Potentially, midkine may be used in the differentiation of SIRS from sepsis, and the identification of Gram-positive sepsis and patients with sepsis who are susceptible to cardiovascular insufficiency and shock (99).

Leptin, a hormone mainly produced by adipocytes, functions primarily in the hypothalamus to control body weight and energy expenditure. Leptin is also involved in cell-mediated immunity and cytokine crosstalk. It has been established that there is a serum threshold (38 mg/l) of leptin between sepsis and non-infectious SIRS (100). Therefore, leptin is another potential biomarker to distinguish sepsis from SIRS.

Procalcitonin is a peptide precursor of calcitonin, which is involved in calcium homeostasis. It has been demonstrated that the serum levels of procalcitonin rise dramatically in a response to bacterial infection (101). Thus, measurement of procalcitonin could be used as a marker of severe sepsis caused by bacteria (102). Procalcitonin also has the greatest sensitivity and specificity for differentiating patients with SIRS from those with sepsis, when compared with IL-2, IL-6, IL-8 and TNF-α (103). Currently, procalcitonin assays are widely used in the clinical setting (104) although there are some limitations, such as the induction of procalcitonin expression by non-infectious disease conditions (105).

An assay of nine biomarkers in the blood obtained from 971 emergency department patients demonstrated that a

Table II. *Outline of sepsis treatment.*

Method	Function	Treatment in animal models	Clinical trial in patients with sepsis
Corticosteroids	Suppress cytokine production		Reduced mortality
Hemodiafiltration	Removes cytokines		Restored blood pressure and respiratory function
Androstenediol	Reduces cytokine production	Increases survival	Unknown
Benzylsulfone derivatives	Suppress cytokine production	Increases survival	Unknown
Soluble TNF-α receptor	Blocks TNF-α activity	Reduces mortality	No beneficial effects
TNF-α neutralizing antibody	Blocks TNF-α activity	Reduces morbidity and mortality	No beneficial effects
IL-17A neutralizing antibody	Blocks IL-17 activity	Improves survival	Unclear
IL-18 neutralizing antibody	Blocks IL-18 activity	Reduces lung injury	Unknown
IL-10 neutralizing antibody	Blocks IL-10 activity	Improves survival	Unknown
GM-CSF	Relieves immunosuppression		Improved clinical parameters, but not survival

IL: Interleukin; GM-CSF: granulocyte-macrophage colony-stimulating factor; TNF: tumor necrosis factor.

biomarker panel of neutrophil gelatinase-associated lipocalin, IL-1Ra, and protein C could be used to predict severe sepsis, septic shock, and death in the patients with suspected sepsis (106). Further study, however, is necessary to prospectively validate the clinical utility of these biomarkers.

It has been reported that the serum levels of IL-1β, IL-6, IL-8, and TNF-α were significantly increased in the new-born patients with sepsis than the control groups and were significantly decreased at the seventh day after antibiotic treatment (107). Thus, serum levels of IL-1β, IL-6, IL-8, and TNF-α may be used in the diagnosis and the assessment of the therapeutic efficiency of neonatal sepsis (107).

IL-8 and MCP-1 displayed the best association with the sequential organ failure assessment (SOFA) scores of patients with sepsis on day 1. In addition, the concentrations of IL-6, IL-8 and G-CSF during the first 24 h were used to predict worsening organ dysfunction or failure of organ dysfunction to improve on day three. Furthermore, several cytokines such as IL-1β, IL-4, IL-6, IL-8, MCP-1 and G-CSF were used to predict early mortality (<48 h), whereas IL-8 and MCP-1 were used in the prediction of mortality at 28 days. A multivariate analysis indicated that MCP-1 was independently coupled with sepsis prognosis (39). Thus, a multiple cytokine assay platform might be developed to identify distinct cytokine profiles, which are linked with sepsis severity, evolution of organ failure and death.

Cytokines in Sepsis Treatment

As stated above, sepsis is characterized by the excessive production of cytokines in the circulating blood, leading to a systematic inflammatory response. Therefore, inhibition of excessive cytokine production or removal of cytokines and other inflammatory mediators from the blood may suppress systemic inflammation during sepsis and improve patient outcomes (Table II).

It has been documented that corticosteroids inhibit transcription factors, such as NF-κB and activator protein 1 (AP-1), and thus suppress cytokine production (108). Clinical trials demonstrated that treatment with long courses of low doses of corticosteroids significantly reduced mortality in patients with severe sepsis and septic shock (109).

Specific devices and techniques are being developed to remove cytokines in the blood in order to treat patients with sepsis. Continuous hemodiafiltration (CHDF) using a polymethylmethacrylate (PMMA) membrane hemofilter (PMMA-CHDF) may effectively remove various cytokines from the circulating blood (110). The hemofilter membrane can absorb many cytokines including IL-6, IL-8, IL-10 and TNF-α. Use of PMMA-CHDF also restored blood pressure, reduced monocytic human leukocyte antigen DR (HLA-DR) expression, and inhibited the delayed neutrophil apoptosis in patients with sepsis. Thus, cytokine removal with PMMA-CHDF may be effective in clinical care (111). Hemofiltration with an immobilized polymyxin-B fiber (PMX) column can also remove cytokines, such as IL-6, IL-10 and TNF-α, from the blood. After treatment with a PMX column, respiratory function was recovered, and SOFA scores improved in patients with sepsis (112).

Attempts have also been made to develop agents that specifically reduce levels of cytokines and other inflammatory mediators in order to treat sepsis. Ulinastatin (UTI), a human protease inhibitor, selectively reduces excessive production of pro-inflammatory cytokines. It has been reported that UTI administration effectively suppressed the levels of TNF-α and IL-6 in septic rats (78), suggesting that UTI may have a therapeutic role for patients with sepsis by inhibiting TNF-α and IL-6. Androstenediol is a

metabolite of dehydroepiandrosterone. Administration of androstenediol also significantly reduced the plasma levels of IL-6 and TNF-α in rats following trauma-hemorrhage (T-H) and CLP for sepsis (113). After treatment with androstenediol, the survival rate improved in septic rats. These results indicate that androstenediol may represent a novel and useful agent in sepsis treatment.

Using soluble cytokine receptor or neutralizing antibodies, researchers have also attempted to develop specific blockade of pro-inflammatory cytokines to reduce infection, morbidity and mortality in sepsis. Use of TNF-α or IL-1 neutralizing antibodies has been shown to block cytokine functions, and thus reduce infection and inflammation in animal models (114). Soluble surface receptors of TNF-α and IL-1 may bind their respective cytokines and inhibit cytokine function. Animal model studies indicated that soluble TNF and IL-1 surface receptors ameliorate septic processes (114). Clinical trials, however, indicated that treatments by TNF-neutralizing antibodies, soluble TNF receptors and IL-1 receptor antagonist did not have any beneficial effects for patients with sepsis (115, 116).

Since augmented IL-17A levels have detrimental effects on mice with sepsis, neutralization of IL-17A by antibodies caused a striking attenuation of bacteremia, reduced plasma levels of pro-inflammatory cytokines, and improved survival rates when the treatment was administered at 12 h after the initiation of experimental sepsis in mice (117). However, the role of IL-17 in patients with sepsis is controversial. Recently, it has been reported that IL-17A and IL-17F mRNA are undetected in peripheral blood mononuclear cells from patients with sepsis (118). A multiplex analysis in 60 patients with severe sepsis showed that IL-17 was not detected (39). Therefore, it is unclear if IL-17 neutralization is a useful therapeutic intervention for patients with sepsis (1, 119).

Several studies have shown that elevated plasma levels of IL-18 are associated with poor clinical outcome in severe inflammatory and septic conditions (41, 42). Caspase-1 intervention or IL-18-binding protein may neutralize IL-18 biologically. Experimental data show that such biological neutralization of IL-18 may be a promising therapeutic approach in treatment of sepsis (120), however, further studies will be required to evaluate their full potential in the treatment of human sepsis (42).

A series of cyclohexene derivatives have been synthesized and tested for their inhibition of cytokines in order to develop an anti-sepsis agent. It has been reported that benzylsulfone derivatives, (*R*)-(+)-10a and (6*R*, 1*S*)-(+)-22a, not only significantly suppress the production of inflammatory cytokines such as TNF-α and IL-6 *in vitro*, but also protected mice from LPS-induced lethality in a dose-dependent manner (121). The results suggest that these agents may be effective in the treatment of sepsis in patients.

Considering the immunosuppression status in patients with sepsis, cytokine immunotherapy is also used in clinical trials of sepsis treatment. Meisel and co-workers reported the results of a randomized, double-blind, placebo-controlled, multicenter trial of GM-CSF immunotherapy in patients with sepsis and sepsis-associated immunosuppression (122). GM-CSF treatment improved clinical parameters in patients with sepsis and sepsis-associated immunosuppression. The treatment was well-tolerated, but did not improve survival rates. Nevertheless, this study was the first biomarker-guided immunostimulatory treatment trial in patients with sepsis (123).

Neutralizing antibodies have also been tested in the development of specific blockade of anti-inflammatory cytokines to reduce immunosuppression in sepsis. It has been reported that neutralization of IL-10 restored IL-18R expression on liver NK cells and re-established IFN-γ response in septic mice, thereby leading to an improved survival (124). Neutralization of IL-10 may also reduce the percentage of $CD4^+CD25^+Foxp3^+$ regulatory T-cells in septic mice and thus improve survival (125). The results suggested that neutralizing IL-10 might represent a novel strategy for treating the immunosuppressive conditions in patients with sepsis.

Cytokine Signaling in Sepsis

It has been reported that there is an significant increase in IL-1β level as early as 12 h, IL-10 as early as 6 h, and TNF-α as early as 6 h in brain extracts after sepsis induction in mice (126). The results demonstrated that cytokine production in the brain is an early event during sepsis. Early production of cytokines may participate both in central nervous system (CNS) dysfunction and brain-blood barrier (BBB) permeability alterations. Therefore, the brain inflammatory response may play a role in the pathophysiology of sepsis.

It has been shown that abnormalities in cytokine receptor signaling pathways are responsible for inflammatory diseases (127). Thus, signal transduction pathways involved in cytokine production may also play an important role in sepsis. Bacterial endotoxins may induce tyrosine phosphorylation of STAT3 (128). Activated STAT3 induces NF-κB translocation and thus triggers cytokine production (129). Stattic, a STAT3 Inhibitor, was found to suppress STAT3 tyrosine phosphorylation *in vivo*, inhibit systemic inflammation, and thus increase mouse survival in experimental sepsis (130). These results indicate that the STAT3 signaling pathway has implications in sepsis.

Bacterial-induced TLR signaling may also be involved in cytokine production in sepsis. Bacterial endotoxins such as LPS bind to TLR, leading to the activation of the small guanosine triphosphate hydrolase (GTPase) ras-related C3 botulinum toxin substrate 1 (RAC1). Activated RAC1 in turn

induces the activation of c-Jun N-terminal kinase (JNK), NF-κB and AP-1. Then, activated NF-κB and AP-1 bind to the promoters of inflammatory cytokines, leading to massive cytokine production in sepsis (131).

Cytokines usually bind their specific receptors, induce signaling pathways and thus regulate immune responses and other cell functions. Therefore, cytokine signaling plays an important role in immune response. For instance, IL-6 binds its unique IL-6Rα receptor and activates the signal transducer Gp130, leading to the activation of the Janus kinase (JAK)/STAT and mitogen-activated protein kinase (MAPK) cascades. In the JAK/STAT pathway, IL-6 binding to its receptor activates JAK tyrosine kinase family members, and then induces the activation of transcription factors of the STAT family. IL-6 mainly activates STAT3, and to a minor extent STAT1. STAT3 controls a number of cellular pathways which are involved in the regulation of cytokine production, cell-cycle progression, apoptosis, tumor angiogenesis, invasion and metastasis (132). IL-6 also leads to activation of the phosphatidylinositide 3-kinases (PI3K)/Akt ("Ak" refers to mouse Ak strain developing spontaneous thymic lymphomas, and "t" stands for thymoma) pathway, which is essential for the anti-apoptotic effect of IL-6 (133).

IL-10 binds to IL-10 receptor (IL-10R) to induce signal pathways and a series of immune responses. IL-10R is a tetramer, comprising of two IL-10R1 polypeptide chains and two IL-10R2 chains. IL-10 binds to the extracellular domain of IL-10R1, leading to the phosphorylation and activation of the receptor-associated Janus tyrosine kinases, JAK1 and tyrosine kinase-2 (Tyk2). After activation, Janus tyrosine kinases induce the phosphorylation of specific tyrosine residues (Y446 and Y496) on the intracellular domain of IL-10R1, resulting in IL-10R1 activation. Then, phosphorylated IL-10R1 activates STAT3 (134). After binding to its receptor, IL-10 may also induce activation of MAPK cascades (135). MAPK cascades are involved in many immune functions (136). For example, activated p38 MAPK suppresses IL-27 production (137). A signaling pathway consisting of MAPK kinase kinase-1 (MEKK1), JNK1 and E3 ubiquitin-protein ligase Itchy homolog (Itch) inhibits Th2 cytokine production and is indispensable for Th2 cell-mediated tolerance induction (138).

TNF-α has two receptors, TNFR1 and TNFR2. TNFR1 is present in most tissues, and both the membrane-bound and soluble forms of TNF-α can bind and activate TNFR1. TNFR2, however, is expressed exclusively in immune cells, and only the membrane-bound form of TNF-α can bind and activate TNFR2. The information about TNF-α signaling is derived from TNFR1, and the role of TNFR2 is still unclear. TNF-α binds to TNFR1, leading to the activation of NF-κB pathway, MAPK cascades and death signaling (139). In the death signaling, activated TNFR1 induces the binding of adaptor protein tumor necrosis factor receptor type 1-associated death domain protein (TRADD) to Fas-associated protein with death domain (FADD), which activates caspase-8. Activated caspase-8 induces its autoproteolytic activity, resulting in the cleavage of effector caspases and induction of cell apoptosis.

In summary, cytokine signaling plays an important role both in cytokine production and cytokine function. Cytokine signaling may also play a role in sepsis. Blockage of specific cytokine signaling pathways may be beneficial in sepsis treatment. Further studies are needed to help understand the role of cytokine signaling in sepsis.

Cytokine Gene Polymorphisms in Sepsis

As stated above, cytokines play a pivotal role in sepsis. Because cytokine gene polymorphisms are involved in the control of cytokine production, it is becoming clear that genetic predisposition plays a critical role in the pathophysiology of sepsis.

Analysis of gene polymorphisms in patients treated with transthoracic esophagectomy without neoadjuvant treatment showed there to be a significantly greater frequency of postoperative infections in the patients carrying the INF-γ 874 (rs2430561) A/A and A/T genotypes. Univariate and multivariate logistic regression models also demonstrated that patients having the INF-γ 874A/T genotype were highly susceptible for the development of postoperative infectious complications (140). These findings suggest that the IFN-γ 874A>T polymorphism may be used in the assessment of risk for patients undergoing esophagectomy for thoracic esophageal cancer of having postoperative infections. This polymorphism may therefore have important clinical relevance in sepsis.

It has been documented that IL-6 is the key cytokine in the pathophysiology of severe sepsis (13, 18, 19). Thus, it is not surprising that the IL-6 -174 G/C promoter genotype is associated with septic shock and IL-6 secretion (141). A recent study, however, demonstrated that there were neither significant differences in the IL-6 -174G/C genotypic frequencies among burn patients with and without sepsis, and healthy individuals nor significant associations between IL-6 genotypes and the serum cytokine levels (142). Further experiments will be necessary to determine if *IL-6* gene polymorphisms play a role in sepsis.

IL-4 may play a role in the pathophysiology of sepsis (66). It has been shown that the -589T/C polymorphism in *IL-4* promoter may alter IL-4 expression and susceptibility to inflammatory or autoimmune diseases. The IL-4/-589C allele was significantly associated with higher plasma IL-4 level and lower IFN-γ production after LPS stimulation, signifying its effect on the regulation of Th1/Th2 balance. Moreover, homozygosity and heterozygosity for this polymorphism were linked with an increased susceptibility

for sepsis (143). These results suggest that the IL-4 -589T/C polymorphism may regulate Th1/Th2 balance and increase susceptibility to sepsis.

Analysis of the -1082A/G polymorphism in the *IL-10* gene promoter demonstrated that the A/A genotype was associated with lower IL-10 production in LPS-stimulated peripheral blood mononuclear cells (PBMCs) from healthy donors. LPS-stimulated PBMCs from the carriage of at least one copy of the IL-10-1082 G allele in patients with sepsis and in healthy controls had a statistically significant increase in IL-10 production. Importantly, as compared with healthy controls, the frequency of the A allele was greater in patients with severe sepsis, whereas surviving patients had a significant lower frequency of G allele. There was an association between increased IL-10 production and poor outcome of sepsis (144). These results indicated that the A allele of the -1082 polymorphism in the IL-10 gene promoter is related to sepsis susceptibility, whereas the G allele is related to increased IL-10 production and higher mortality in sepsis.

Examination of IL-1Ra gene polymorphism demonstrated that there was a significant association between IL-1Ra allele *2 gene polymorphism and survival of patients with sepsis. As compared with patients homozygous or heterozygous for allele *1, PBMCs from homozygotes for IL-1Ra allele *2 produced significantly lower levels of IL-1Ra (145). The results suggested that insufficient production of IL-Ra due to gene polymorphism may contribute to the higher mortality rate in patients with sepsis.

Analysis of polymorphism in the *TNF-α* gene promoter revealed that there was no association between TNF-α gene polymorphism and sepsis (146). A recent study, however, demonstrated that TNF-308 polymorphism (rs1800629) was associated with mortality and ventilator duration in patients with sepsis (147), suggesting that *TNF-α* gene polymorphisms may play a role in sepsis.

TLRs are a class of proteins that play a key role in the innate immune system. In response to microbes, TLRs are involved in cytokine production and cellular activation (148). It has been reported that *TLR1* gene polymorphisms correlated with whole-blood hyper-inflammatory responses to pathogen-associated molecules, sepsis-associated multiorgan dysfunction and acute lung injury (149). Moreover, *TLR2* single nucleotide polymorphism Arg753Gln was associated with increased plasma TNF-α concentrations, but reduced IFN-γ and IL-8 levels in Candida sepsis (150). Thus, TLR gene polymorphisms may also contribute to the pathophysiology of sepsis.

Conclusion

Sepsis triggers the production of a diverse array of cytokines that are pro-inflammatory and anti-inflammatory. While pro-inflammatory cytokines are necessary for controlling infection, their excessive production may lead to tissue and organ injury. Similarly, the anti-inflammatory cytokines are critical in regulating the overall immune response and in establishing homeostasis. Therefore, their dysregulation can also trigger pathogenesis. Together, these studies indicate that an imbalance of pro- and anti-inflammatory cytokines produced during sepsis may play an important role in pathogenesis. While clinical and experimental studies have identified some critical roles played by individual cytokines, a combined signature profile of cytokines involved in sepsis is necessary to understand the mechanisms at play and offer better treatment approaches. Such a profile may also help identify biomarkers of sepsis and prognosis. Effective removal of pathogenic cytokines and administration of protective cytokines may be helpful in successful treatment of sepsis. Overall, studies on cytokines in sepsis have great implications in the understanding of pathophysiology and the development of effective treatment modalities against sepsis.

Acknowledgements

This study was supported by NIH grants R01ES019313, R01MH094755, P01AT003961, R01AT006888 and VA Merit Award I01BX001357.

References

1 Rittirsch D, Flierl MA and Ward PA: Harmful molecular mechanisms in sepsis. Nat Rev Immunol *8(10)*: 776-787, 2008.
2 Studnek JR, Artho MR, Garner CL Jr. and Jones AE: The impact of emergency medical services on the ed care of severe sepsis. Am J Emerg med *30(1)*: 51-56, 2012.
3 Hanisch E, Brause R, Paetz J and Arlt B: Review of a large clinical series: Predicting death for patients with abdominal septic shock. J Intensive Care Med *26(1)*: 27-33, 2011.
4 Becker KL, Snider R and Nylen ES: Procalcitonin in sepsis and systemic inflammation: A harmful biomarker and a therapeutic target. Br J Pharmacol *159(2)*: 253-264, 2010.
5 Melamed A and Sorvillo FJ: The burden of sepsis-associated mortality in the united states from 1999 to 2005: An analysis of multiple-cause-of-death data. Crit Care *13(1)*: R28, 2009.
6 Unsinger J, McGlynn M, Kasten KR, Hoekzema AS, Watanabe E, Muenzer JT, McDonough JS, Tschoep J, Ferguson TA, McDunn JE, Morre M, Hildeman DA, Caldwell CC and Hotchkiss RS: Il-7 promotes t cell viability, trafficking, and functionality and improves survival in sepsis. J Immunol *184(7)*: 3768-3779, 2010.
7 Brun-Buisson C: Epidemiology of severe sepsis. Presse Med *35(3)*: 513-520, 2006.
8 Le Gall JR, Alberti C and Brun Buisson C: Epidemiology of infection and sepsis in intensive care unit patients. Bull Acad Natl Med *188(7)*: 1115-1125, 2004.
9 Russell JA: Management of sepsis. N Eng J Med *355(16)*: 1699-1713, 2006.
10 Meakins JL, Pietsch JB, Bubenick O, Kelly R, Rode H, Gordon J and MacLean LD: Delayed hypersensitivity: Indicator of acquired failure of host defenses in sepsis and trauma. Ann Surg *186(3)*: 241-250, 1977.

11 Boomer JS, To K, Chang KC, Takasu O, Osborne DF, Walton AH, Bricker TL, Jarman SD, 2nd, Kreisel D, Krupnick AS, Srivastava A, Swanson PE, Green JM and Hotchkiss RS: Immunosuppression in patients who die of sepsis and multiple organ failure. JAMA *306(23)*: 2594-2605, 2011.

12 Hotchkiss RS, Swanson PE, Freeman BD, Tinsley KW, Cobb JP, Matuschak GM, Buchman TG and Karl IE: Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. Crit Care Med *27(7)*: 1230-1251, 1999.

13 Mera S, Tatulescu D, Cismaru C, Bondor C, Slavcovici A, Zanc V, Carstina D and Oltean M: Multiplex cytokine profiling in patients with sepsis. APMIS *119(2)*: 155-163, 2011.

14 Jones SA, Scheller J and Rose-John S: Therapeutic strategies for the clinical blockade of IL-6/gp130 signaling. J Clin Invest *121(9)*: 3375-3383, 2011.

15 Lukaszewicz M, Mroczko B and Szmitkowski M: Clinical significance of interleukin-6 (IL-6) as a prognostic factor of cancer disease. Pol Arch Med Wewn *117(5-6)*: 247-251, 2007 (in Polish).

16 Patterson CC, Smith AE, Yarnell JW, Rumley A, Ben-Shlomo Y and Lowe GD: The associations of interleukin-6 (IL-6) and downstream inflammatory markers with risk of cardiovascular disease: The caerphilly study. Atherosclerosis *209(2)*: 551-557, 2010.

17 Ishihara K and Hirano T: IL-6 in autoimmune disease and chronic inflammatory proliferative disease. Cytokine Growth Factor Rev *13(4-5)*: 357-368, 2002.

18 Gouel-Cheron A, Allaouchiche B, Guignant C, Davin F, Floccard B and Monneret G: Early interleukin-6 and slope of monocyte human leukocyte antigen-DR: A powerful association to predict the development of sepsis after major trauma. PloS one *7(3)*: e33095, 2012.

19 Wu HP, Chen CK, Chung K, Tseng JC, Hua CC, Liu YC, Chuang DY and Yang CH: Serial cytokine levels in patients with severe sepsis. Inflamm Res *58(7)*: 385-393, 2009.

20 Kellum JA, Kong L, Fink MP, Weissfeld LA, Yealy DM, Pinsky MR, Fine J, Krichevsky A, Delude RL and Angus DC: Understanding the inflammatory cytokine response in pneumonia and sepsis: Results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. Arch Intern Med *167(15)*: 1655-1663, 2007.

21 Kumar AT, Sudhir U, Punith K, Kumar R, Ravi Kumar VN and Rao MY: Cytokine profile in elderly patients with sepsis. Ind J Crit Care Med *13(2)*: 74-78, 2009.

22 Strieter RM, Polverini PJ, Kunkel SL, Arenberg DA, Burdick MD, Kasper J, Dzuiba J, Van Damme J, Walz A, Marriott D, Chan SY, Roczniak S and Shanafelt AB: The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. J Biol Chem *270(45)*: 27348-27357, 1995.

23 Lee YS, Bak EJ, Kim M, Park W, Seo JT and Yoo YJ: Induction of IL-8 in periodontal ligament cells by H2O2. J Microbiol *46(5)*: 579-584, 2008.

24 Glowacka E, Lewkowicz P, Rotsztejn H and Zalewska A: IL-8, IL-12 and IL-10 cytokines generation by neutrophils, fibroblasts and neutrophils- fibroblasts interaction in psoriasis. Adv Med Sci *55(2)*: 254-260, 2010.

25 Livaditi O, Kotanidou A, Psarra A, Dimopoulou I, Sotiropoulou C, Augustatou K, Papasteriades C, Armaganidis A, Roussos C, Orfanos SE and Douzinas EE: Neutrophil CD64 expression and serum IL-8: Sensitive early markers of severity and outcome in sepsis. Cytokine *36(5-6)*: 283-290, 2006.

26 Hsieh CS, Macatonia SE, Tripp CS, Wolf SF, O'Garra A and Murphy KM: Development of Th1 CD4+ T cells through IL-12 produced by listeria-induced macrophages. Science *260(5107)*: 547-549, 1993.

27 Seder RA, Kelsall BL and Jankovic D: Differential roles for IL-12 in the maintenance of immune responses in infectious *versus* autoimmune disease. J Immunol *157(7)*: 2745-2748, 1996.

28 Hu Y, Shen F, Crellin NK and Ouyang W: The IL-17 pathway as a major therapeutic target in autoimmune diseases. Ann NY Acad Sci *1217*: 60-76, 2011.

29 Shahrara S, Pickens SR, Mandelin AM, 2nd, Karpus WJ, Huang Q, Kolls JK and Pope RM: IL-17-mediated monocyte migration occurs partially through CC chemokine ligand 2/monocyte chemoattractant protein-1 induction. J Immunol *184(8)*: 4479-4487, 2010.

30 Witowski J, Pawlaczyk K, Breborowicz A, Scheuren A, Kuzlan-Pawlaczyk M, Wisniewska J, Polubinska A, Friess H, Gahl GM, Frei U and Jorres A: IL-17 stimulates intraperitoneal neutrophil infiltration through the release of gro alpha chemokine from mesothelial cells. J Immunol *165(10)*: 5814-5821, 2000.

31 Costa VS, Mattana TC and da Silva ME: Unregulated IL-23/IL-17 immune response in autoimmune diseases. Diabetes Res Clin Pract *88(3)*: 222-226, 2010.

32 Reynolds JM, Angkasekwinai P and Dong C: IL-17 family member cytokines: Regulation and function in innate immunity. Cytokine Growth Factor Rev *21(6)*: 413-423, 2010.

33 Chakir J, Shannon J, Molet S, Fukakusa M, Elias J, Laviolette M, Boulet LP and Hamid Q: Airway remodeling-associated mediators in moderate to severe asthma: Effect of steroids on TGF-beta, IL-11, IL-17, and type I and type III collagen expression. J Allergy Clin Immunol *111(6)*: 1293-1298, 2003.

34 Wang YH and Liu YJ: The IL-17 cytokine family and their role in allergic inflammation. Curr Opin Immunol *20(6)*: 697-702, 2008.

35 Crome SQ, Wang AY and Levings MK: Translational mini-review series on Th17 cells: Function and regulation of human T helper 17 cells in health and disease. Clin Exp Immunol *159(2)*: 109-119, 2010.

36 Aggarwal S and Gurney AL: IL-17: Prototype member of an emerging cytokine family. J Leuk Biol *71(1)*: 1-8, 2002.

37 van de Veerdonk FL, Kullberg BJ, Verschueren IC, Hendriks T, van der Meer JW, Joosten LA and Netea MG: Differential effects of IL-17 pathway in disseminated candidiasis and zymosan-induced multiple organ failure. Shock *34(4)*: 407-411, 2010.

38 Freitas A, Alves-Filho JC, Victoni T, Secher T, Lemos HP, Sonego F, Cunha FQ and Ryffel B: IL-17 receptor signaling is required to control polymicrobial sepsis. J Immunol *182(12)*: 7846-7854, 2009.

39 Bozza FA, Salluh JI, Japiassu AM, Soares M, Assis EF, Gomes RN, Bozza MT, Castro-Faria-Neto HC and Bozza PT: Cytokine profiles as markers of disease severity in sepsis: A multiplex analysis. Crit Care *11(2)*: R49, 2007.

40 Boraschi D and Dinarello CA: IL-18 in autoimmunity: Review. Eur Cytokine Netw *17(4)*: 224-252, 2006.

41 Rau M, Schiller M, Krienke S, Heyder P, Lorenz H and Blank N: Clinical manifestations but not cytokine profiles differentiate adult-onset still's disease and sepsis. J Rheumatol *37(11)*: 2369-2376, 2010.

42 Tschoeke SK, Oberholzer A and Moldawer LL: Interleukin-18: A novel prognostic cytokine in bacteria-induced sepsis. Crit Care Med *34(4)*: 1225-1233, 2006.

43 Schoenborn JR and Wilson CB: Regulation of interferon-gamma during innate and adaptive immune responses. Adv Immunol *96*: 41-101, 2007.

44 Stassen NA, Leslie-Norfleet LA, Robertson AM, Eichenberger MR and Polk HC Jr.: Interferon-gamma gene polymorphisms and the development of sepsis in patients with trauma. Surgery *132(2)*: 289-292, 2002.

45 Romero CR, Herzig DS, Etogo A, Nunez J, Mahmoudizad R, Fang G, Murphey ED, Toliver-Kinsky T and Sherwood ER: The role of interferon-gamma in the pathogenesis of acute intra-abdominal sepsis. J Leuk Biol *88(4)*: 725-735, 2010.

46 Weighardt H, Heidecke CD, Emmanuilidis K, Maier S, Bartels H, Siewert JR and Holzmann B: Sepsis after major visceral surgery is associated with sustained and interferon-gamma-resistant defects of monocyte cytokine production. Surgery *127(3)*: 309-315, 2000.

47 Ono S, Ueno C, Aosasa S, Tsujimoto H, Seki S and Mochizuki H: Severe sepsis induces deficient interferon-gamma and interleukin-12 production, but interleukin-12 therapy improves survival in peritonitis. Am J Surg *182(5)*: 491-497, 2001.

48 Ertel W, Morrison MH, Ayala A, Dean RE and Chaudry IH: Interferon-gamma attenuates hemorrhage-induced suppression of macrophage and splenocyte functions and decreases susceptibility to sepsis. Surgery *111(2)*: 177-187, 1992.

49 Hamilton JA: GM-CSF in inflammation and autoimmunity. Trends Immunol *23(8)*: 403-408, 2002.

50 Hamilton JA and Anderson GP: GM-CSF biology. Growth Factors *22(4)*: 225-231, 2004.

51 Lendemans S, Kreuzfelder E, Waydhas C, Schade FU and Flohe S: Differential immunostimulating effect of granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF) and interferon gamma (IFNgamma) after severe trauma. Inflamm Res *56(1)*: 38-44, 2007.

52 Orozco H, Arch J, Medina-Franco H, Pantoja JP, Gonzalez QH, Vilatoba M, Hinojosa C, Vargas-Vorackova F and Sifuentes-Osornio J: Molgramostim (GM-CSF) associated with antibiotic treatment in nontraumatic abdominal sepsis: A randomized, double-blind, placebo-controlled clinical trial. Arch Surg *141(2)*: 150-153, 2006.

53 Bo L, Wang F, Zhu J, Li J and Deng X: Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: A meta-analysis. Crit Care *15(1)*: R58, 2011.

54 Wallach D: Cell death induction by TNF: A matter of self control. Trends Biochem Sci *22(4)*: 107-109, 1997.

55 Scheringa M and Marquet RL: TNF: A brief review with emphasis on its antitumor activity. Biotherapy *2(3)*: 275-281, 1990.

56 Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK and Lanctot KL: A meta-analysis of cytokines in major depression. Biol Psychiatry *67(5)*: 446-457, 2010.

57 Swardfager W, Lanctot K, Rothenburg L, Wong A, Cappell J and Herrmann N: A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry *68(10)*: 930-941, 2010.

58 Locksley RM, Killeen N and Lenardo MJ: The TNF and TNF receptor superfamilies: Integrating mammalian biology. Cell *104(4)*: 487-501, 2001.

59 Huang W, Tang Y and Li L: HMGB1, a potent proinflammatory cytokine in sepsis. Cytokine *51(2)*: 119-126, 2010.

60 London NR, Zhu W, Bozza FA, Smith MC, Greif DM, Sorensen LK, Chen L, Kaminoh Y, Chan AC, Passi SF, Day CW, Barnard DL, Zimmerman GA, Krasnow MA and Li DY: Targeting Robo4-dependent Slit signaling to survive the cytokine storm in sepsis and influenza. Sci Transl Med *2(23)*: 23ra19, 2010.

61 Opal SM and DePalo VA: Anti-inflammatory cytokines. Chest *117(4)*: 1162-1172, 2000.

62 Schreuder H, Tardif C, Trump-Kallmeyer S, Soffientini A, Sarubbi E, Akeson A, Bowlin T, Yanofsky S and Barrett RW: A new cytokine-receptor binding mode revealed by the crystal structure of the IL-1 receptor with an antagonist. Nature *386(6621)*: 194-200, 1997.

63 Dinarello CA: Induction of interleukin-1 and interleukin-1 receptor antagonist. Semin Oncol *24(3 Suppl 9)*: S9-81-S89-93, 1997.

64 Alexander HR, Doherty GM, Venzon DJ, Merino MJ, Fraker DL and Norton JA: Recombinant interleukin-1 receptor antagonist (IL-1Ra): Effective therapy against Gram-negative sepsis in rats. Surgery *112(2)*: 188-193, 1992.

65 Kay AB, Barata L, Meng Q, Durham SR and Ying S: Eosinophils and eosinophil-associated cytokines in allergic inflammation. Int Arch Allergy Immunol *113(1-3)*: 196-199, 1997.

66 Song GY, Chung CS, Chaudry IH and Ayala A: IL-4-induced activation of the Stat6 pathway contributes to the suppression of cell-mediated immunity and death in sepsis. Surgery *128(2)*: 133-138, 2000.

67 Surbatovic M, Filipovic N, Radakovic S, Stankovic N and Slavkovic Z: Immune cytokine response in combat casualties: Blast or explosive trauma with or without secondary sepsis. Mil Med 172(2): 190-195, 2007.

68 Hultgren O, Kopf M and Tarkowski A: Outcome of *Staphylococcus aureus*-triggered sepsis and arthritis in IL-4-deficient mice depends on the genetic background of the host. Eur J Immunol *29(8)*: 2400-2405, 1999.

69 Gogos CA, Drosou E, Bassaris HP and Skoutelis A: Pro- *versus* anti-inflammatory cytokine profile in patients with severe sepsis: A marker for prognosis and future therapeutic options. J Infect Dis *181(1)*: 176-180, 2000.

70 Neddermann P, Graziani R, Ciliberto G and Paonessa G: Functional expression of soluble human interleukin-11 (IL-11) receptor alpha and stoichiometry of *in vitro* IL-11 receptor complexes with gp130. J Biol Chem *271(48)*: 30986-30991, 1996.

71 Hill GR, Cooke KR, Teshima T, Crawford JM, Keith JC Jr., Brinson YS, Bungard D and Ferrara JL: Interleukin-11 promotes T cell polarization and prevents acute graft-*versus*-host disease after allogeneic bone marrow transplantation. J Clin Invest *102(1)*: 115-123, 1998.

72 Chang M, Williams A, Ishizawa L, Knoppel A, van de Ven C and Cairo MS: Endogenous interleukin-11 (IL-11) expression is increased and prophylactic use of exogenous IL-11 enhances platelet recovery and improves survival during thrombocytopenia associated with experimental group B streptococcal sepsis in neonatal rats. Blood Cells Mol Dis *22(1)*: 57-67, 1996.

73 Opal SM, Keith JC Jr., Jhung J, Palardy JE, Parejo N, Marchese E and Maganti V: Orally administered recombinant human interleukin-11 is protective in experimental neutropenic sepsis. J Infect Dis *187(1)*: 70-76, 2003.

74 Wynn TA: IL-13 effector functions. Annu Rev Immunol *21*: 425-456, 2003.
75 Callard RE, Matthews DJ and Hibbert L: IL-4 and IL-13 receptors: Are they one and the same? Immunol Today *17(3)*: 108-110, 1996.
76 de Waal Malefyt R, Figdor CG, Huijbens R, Mohan-Peterson S, Bennett B, Culpepper J, Dang W, Zurawski G and de Vries JE: Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-gamma or IL-10. J Immunol *151(11)*: 6370-6381, 1993.
77 Muchamuel T, Menon S, Pisacane P, Howard MC and Cockayne DA: IL-13 protects mice from lipopolysaccharide-induced lethal endotoxemia: Correlation with down-modulation of TNF-alpha, IFN-gamma, and IL-12 production. J Immunol *158(6)*: 2898-2903, 1997.
78 Cao YZ, Tu YY, Chen X, Wang BL, Zhong YX and Liu MH: Protective effect of ulinastatin against murine models of sepsis: Inhibition of TNF-alpha and IL-6 and augmentation of IL-10 and IL-13. Exp Toxicol Pathol *64(6)*: 543-547, 2012.
79 van der Poll T, de Waal Malefyt R, Coyle SM and Lowry SF: Antiinflammatory cytokine responses during clinical sepsis and experimental endotoxemia: Sequential measurements of plasma soluble interleukin (IL)-1 receptor type II, IL-10, and IL-13. J Infect Dis *175(1)*: 118-122, 1997.
80 Collison LW, Workman CJ, Kuo TT, Boyd K, Wang Y, Vignali KM, Cross R, Sehy D, Blumberg RS and Vignali DA: The inhibitory cytokine IL-35 contributes to regulatory T-cell function. Nature *450(7169)*: 566-569, 2007.
81 Collison LW, Delgoffe GM, Guy CS, Vignali KM, Chaturvedi V, Fairweather D, Satoskar AR, Garcia KC, Hunter CA, Drake CG, Murray PJ and Vignali DA: The composition and signaling of the IL-35 receptor are unconventional. Nat Immunol *13(3)*: 290-299, 2012.
82 Niedbala W, Wei XQ, Cai B, Hueber AJ, Leung BP, McInnes IB and Liew FY: IL-35 is a novel cytokine with therapeutic effects against collagen-induced arthritis through the expansion of regulatory T cells and suppression of Th17 cells. Eur J Immunol *37(11)*: 3021-3029, 2007.
83 Chaturvedi V, Collison LW, Guy CS, Workman CJ and Vignali DA: Cutting edge: Human regulatory T cells require IL-35 to mediate suppression and infectious tolerance. J Immunol *186(12)*: 6661-6666, 2011.
84 Ayala A, Knotts JB, Ertel W, Perrin MM, Morrison MH and Chaudry IH: Role of interleukin 6 and transforming growth factor-beta in the induction of depressed splenocyte responses following sepsis. Arch Surg *128(1)*: 89-94, 1993.
85 Ahmad S, Choudhry MA, Shankar R and Sayeed MM: Transforming growth factor-beta negatively modulates T-cell responses in sepsis. FEBS Lett *402(2-3)*: 213-218, 1997.
86 Pusterla N, Magdesian KG, Mapes S and Leutenegger CM: Expression of molecular markers in blood of neonatal foals with sepsis. Am J Vet Res *67(6)*: 1045-1049, 2006.
87 Knapp S, Thalhammer F, Locker GJ, Laczika K, Hollenstein U, Frass M, Winkler S, Stoiser B, Wilfing A and Burgmann H: Prognostic value of MIP-1 alpha, TGF-beta 2, sELAM-1, and sVCAM-1 in patients with Gram-positive sepsis. Clin Immunol Immunopathol *87(2)*: 139-144, 1998.
88 Arnalich F, Garcia-Palomero E, Lopez J, Jimenez M, Madero R, Renart J, Vazquez JJ and Montiel C: Predictive value of nuclear factor kappab activity and plasma cytokine levels in patients with sepsis. Infect Immun *68(4)*: 1942-1945, 2000.
89 Liu SF and Malik AB: Nf-kappa B activation as a pathological mechanism of septic shock and inflammation. Am J Physio Lung Cell Mol Physiol *290(4)*: L622-L645, 2006.
90 Finnerty CC, Przkora R, Herndon DN and Jeschke MG: Cytokine expression profile over time in burned mice. Cytokine *45(1)*: 20-25, 2009.
91 Ulloa L and Tracey KJ: The "cytokine profile": A code for sepsis. Trends Mol Med *11(2)*: 56-63, 2005.
92 Finnerty CC, Herndon DN, Chinkes DL and Jeschke MG: Serum cytokine differences in severely burned children with and without sepsis. Shock *27(1)*: 4-9, 2007.
93 Campos DP, Silva MV, Machado JR, Castellano LR, Rodrigues V and Barata CH: Early-onset neonatal sepsis: Cord blood cytokine levels at diagnosis and during treatment. J Pediatr *86(6)*: 509-514, 2010.
94 Abdelhamid AE, Chuang SL, Hayes P and Fell JM: *In vitro* cow's milk protein-specific inflammatory and regulatory cytokine responses in preterm infants with necrotizing enterocolitis and sepsis. Pediatr Res *69(2)*: 165-169, 2011.
95 Opal SM, Girard TD and Ely EW: The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis *41(Suppl 7)*: S504-512, 2005.
96 Castle S, Uyemura K, Wong W, Modlin R and Effros R: Evidence of enhanced type 2 immune response and impaired upregulation of a type 1 response in frail elderly nursing home residents. Mech Ageing Dev *94(1-3)*: 7-16, 1997.
97 Saito H, Sherwood ER, Varma TK and Evers BM: Effects of aging on mortality, hypothermia, and cytokine induction in mice with endotoxemia or sepsis. Mech Ageing Dev *124(10-12)*: 1047-1058, 2003.
98 Opal SM: Endotoxin and cytokine detection systems as biomarkers for sepsis-induced renal injury. Contrib Nephrol *156*: 220-226, 2007.
99 Krzystek-Korpacka M, Mierzchala M, Neubauer K, Durek G and Gamian A: Midkine, a multifunctional cytokine, in patients with severe sepsis and septic shock: A pilot study. Shock *35(5)*: 471-477, 2011.
100 Yousef AA, Amr YM and Suliman GA: The diagnostic value of serum leptin monitoring and its correlation with tumor necrosis factor-alpha in critically ill patients: A prospective observational study. Crit Care *14(2)*: R33, 2010.
101 Charles PE, Ladoire S, Aho S, Quenot JP, Doise JM, Prin S, Olsson NO and Blettery B: Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC Infect Dis *8*: 38, 2008.
102 Nyamande K and Lalloo UG: Serum procalcitonin distinguishes cap due to bacteria, mycobacterium tuberculosis and pjp. Int J Tuberc Lung Dis *10(5)*: 510-515, 2006.
103 Balc IC, Sungurtekin H, Gurses E, Sungurtekin U and Kaptanoglu B: Usefulness of procalcitonin for diagnosis of sepsis in the intensive care unit. Crit Care *7(1)*: 85-90, 2003.
104 Moretti D, Ramirez MM, Settecase CJ, Bagilet DH and Quaglino MB: Usefulness of procalcitonin upon admission to intensive care in the diagnosis and prognosis of sepsis. Med Intensiva *37(3)*: 156-162, 2013.
105 Riedel S: Procalcitonin and the role of biomarkers in the diagnosis and management of sepsis. Diagn Microbiol Infect Dis *73(3)*: 221-227, 2012.

106 Shapiro NI, Trzeciak S, Hollander JE, Birkhahn R, Otero R, Osborn TM, Moretti E, Nguyen HB, Gunnerson KJ, Milzman D, Gaieski DF, Goyal M, Cairns CB, Ngo L and Rivers EP: A prospective, multicenter derivation of a biomarker panel to assess risk of organ dysfunction, shock, and death in emergency department patients with suspected sepsis. Crit Care Med *37(1)*: 96-104, 2009.

107 Kurt AN, Aygun AD, Godekmerdan A, Kurt A, Dogan Y and Yilmaz E: Serum IL-1beta, IL-6, IL-8, and TNF-alpha levels in early diagnosis and management of neonatal sepsis. Mediators Inflamm *2007*: 31397, 2007.

108 Bachert C and Geveart P: Effect of intranasal corticosteroids on release of cytokines and inflammatory mediators. Allergy *54(Suppl 57)*: 116-123, 1999.

109 Annane D, Bellissant E, Bollaert PE, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M and Meduri GU: Corticosteroids in the treatment of severe sepsis and septic shock in adults: A systematic review. JAMA *301(22)*: 2362-2375, 2009.

110 Hirasawa H, Oda S and Matsuda K: Continuous hemodiafiltration with cytokine-adsorbing hemofilter in the treatment of severe sepsis and septic shock. Contrib Nephrol *156*: 365-370, 2007.

111 Nakamura M, Oda S, Sadahiro T, Hirayama Y, Watanabe E, Tateishi Y, Nakada TA and Hirasawa H: Treatment of severe sepsis and septic shock by chdf using a pmma membrane hemofilter as a cytokine modulator. Contrib Nephrol *166*: 73-82, 2010.

112 Zagli G, Bonizzoli M, Spina R, Cianchi G, Pasquini A, Anichini V, Matano S, Tarantini F, Di Filippo A, Maggi E and Peris A: Effects of hemoperfusion with an immobilized polymyxin-B fiber column on cytokine plasma levels in patients with abdominal sepsis. Minerva Anestesiol *76(6)*: 405-412, 2010.

113 Suzuki T, Shimizu T, Szalay L, Choudhry MA, Rue LW, 3rd, Bland KI and Chaudry IH: Androstenediol ameliorates alterations in immune cells cytokine production capacity in a two-hit model of trauma-hemorrhage and sepsis. Cytokine *34(1-2)*: 76-84, 2006.

114 Dinarello CA: The proinflammatory cytokines interleukin-1 and tumor necrosis factor and treatment of the septic shock syndrome. J Infect Dis *163(6)*: 1177-1184, 1991.

115 Clark MA, Plank LD, Connolly AB, Streat SJ, Hill AA, Gupta R, Monk DN, Shenkin A and Hill GL: Effect of a chimeric antibody to tumor necrosis factor-alpha on cytokine and physiologic responses in patients with severe sepsis – a randomized, clinical trial. Crit Care Med *26(10)*: 1650-1659, 1998.

116 Dinarello CA: Proinflammatory cytokines. Chest *118(2)*: 503-508, 2000.

117 Flierl MA, Rittirsch D, Gao H, Hoesel LM, Nadeau BA, Day DE, Zetoune FS, Sarma JV, Huber-Lang MS, Ferrara JL and Ward PA: Adverse functions of IL-17A in experimental sepsis. FASEB J *22(7)*: 2198-2205, 2008.

118 White M, Lawless MW, O'Dwyer MJ, Grealy R, Connell BO, Stordeur P, Kelleher D, McManus R and Ryan T: Transforming growth factor beta-1 and interleukin-17 gene transcription in peripheral blood mononuclear cells and the human response to infection. Cytokine *50(3)*: 322-327, 2010.

119 Bosmann M and Ward PA: Therapeutic potential of targeting IL-17 and IL-23 in sepsis. Clin Transl Med *1(4)*: 1-5, 2012.

120 Dolinay T, Kim YS, Howrylak J, Hunninghake GM, An CH, Fredenburgh L, Massaro AF, Rogers A, Gazourian L, Nakahira K, Haspel JA, Landazury R, Eppanapally S, Christie JD, Meyer NJ, Ware LB, Christiani DC, Ryter SW, Baron RM and Choi AM: Inflammasome-regulated cytokines are critical mediators of acute lung injury. Am J Respir Crit Care Med *185(11)*: 1225-1234, 2012.

121 Yamada M, Ichikawa T, Ii M, Itoh K, Tamura N and Kitazaki T: Novel cyclohexene derivatives as anti-sepsis agents: Synthetic studies and inhibition of no and cytokine production. Bioorg Med Chem *16(7)*: 3941-3958, 2008.

122 Meisel C, Schefold JC, Pschowski R, Baumann T, Hetzger K, Gregor J, Weber-Carstens S, Hasper D, Keh D, Zuckermann H, Reinke P and Volk HD: Granulocyte-macrophage colony-stimu-lating factor to reverse sepsis-associated immuno-suppression: A double-blind, randomized, placebo-controlled multicenter trial. Am J Respir Crit Care Med *180(7)*: 640-648, 2009.

123 Trapnell BC: A novel biomarker-guided immunomodulatory approach for the therapy of sepsis. Am J Respir Crit Care Med *180(7)*: 585-586, 2009.

124 Hiraki S, Ono S, Kinoshita M, Tsujimoto H, Takahata R, Miyazaki H, Saitoh D, Seki S and Hase K: Neutralization of IL-10 restores the downregulation of IL-18 receptor on natural killer cells and interferon-gamma production in septic mice, thus leading to an improved survival. Shock *37(2)*: 177-182, 2012.

125 Hiraki S, Ono S, Tsujimoto H, Kinoshita M, Takahata R, Miyazaki H, Saitoh D and Hase K: Neutralization of interleukin-10 or transforming growth factor-beta decreases the percentages of $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T-cells in septic mice, thereby leading to an improved survival. Surgery *151(2)*: 313-322, 2012.

126 Comim CM, Vilela MC, Constantino LS, Petronilho F, Vuolo F, Lacerda-Queiroz N, Rodrigues DH, da Rocha JL, Teixeira AL, Quevedo J and Dal-Pizzol F: Traffic of leukocytes and cytokine up-regulation in the central nervous system in sepsis. Intensive Care Med *37(4)*: 711-718, 2011.

127 O'Sullivan LA, Liongue C, Lewis RS, Stephenson SE and Ward AC: Cytokine receptor signaling through the Jak-Stat-Socs pathway in disease. Mol Immunol *44(10)*: 2497-2506, 2007.

128 Hosoi T, Okuma Y, Kawagishi T, Qi X, Matsuda T and Nomura Y: Bacterial endotoxin induces STAT3 activation in the mouse brain. Brain Res *1023(1)*: 48-53, 2004.

129 Cho ML, Kang JW, Moon YM, Nam HJ, Jhun JY, Heo SB, Jin HT, Min SY, Ju JH, Park KS, Cho YG, Yoon CH, Park SH, Sung YC and Kim HY: STAT3 and NF-kappab signal pathway is required for IL-23-mediated IL-17 production in spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice. J Immunol *176(9)*: 5652-5661, 2006.

130 Pena G, Cai B, Liu J, van der Zanden EP, Deitch EA, de Jonge WJ and Ulloa L: Unphosphorylated STAT3 modulates alpha 7 nicotinic receptor signaling and cytokine production in sepsis. Eur J Immunol *40(9)*: 2580-2589, 2010.

131 Wen H, Lei Y, Eun SY and Ting JP: Plexin-A4-semaphorin 3A signaling is required for Toll-like receptor- and sepsis-induced cytokine storm. J Exp Med *207(13)*: 2943-2957, 2010.

132 Dauer DJ, Ferraro B, Song L, Yu B, Mora L, Buettner R, Enkemann S, Jove R and Haura EB: Stat3 regulates genes common to both wound healing and cancer. Oncogene *24(21)*: 3397-3408, 2005.

133 Heinrich PC, Behrmann I, Haan S, Hermanns HM, Muller-Newen G and Schaper F: Principles of interleukin (IL)-6-type cytokine signalling and its regulation. Biochem J *374(Pt 1)*: 1-20, 2003.

134 Donnelly RP, Dickensheets H and Finbloom DS: The interleukin-10 signal transduction pathway and regulation of gene expression in mononuclear phagocytes. J Interferon Cytokine Res *19(6)*: 563-573, 1999.

135 Song GY, Chung CS, Schwacha MG, Jarrar D, Chaudry IH and Ayala A: Splenic immune suppression in sepsis: A role for IL-10-induced changes in P38 MAPK signaling. J Surg Res *83(1)*: 36-43, 1999.

136 Huang G, Shi LZ and Chi H: Regulation of JNK and p38 MAPK in the immune system: Signal integration, propagation and termination. Cytokine *48(3)*: 161-169, 2009.

137 Zhang J, Qian X, Ning H, Eickhoff CS, Hoft DF and Liu J: Transcriptional suppression of IL-27 production by *Mycobacterium tuberculosis*-activated p38 MAPK *via* inhibition of AP-1 binding. J Immunol *186(10)*: 5885-5895, 2011.

138 Venuprasad K, Elly C, Gao M, Salek-Ardakani S, Harada Y, Luo JL, Yang C, Croft M, Inoue K, Karin M and Liu YC: Convergence of Itch-induced ubiquitination with MEKK1-JNK signaling in Th2 tolerance and airway inflammation. J Clin Invest *116(4)*: 1117-1126, 2006.

139 Gaur U and Aggarwal BB: Regulation of proliferation, survival and apoptosis by members of the TNF superfamily. Biochem Pharmacol *66(8)*: 1403-1408, 2003.

140 Motoyama S, Miura M, Hinai Y, Maruyama K, Usami S, Nakatsu T, Saito H, Minamiya Y, Murata K, Suzuki T and Ogawa J: Interferon-gamma 874A>T genetic polymorphism is associated with infectious complications following surgery in patients with thoracic esophageal cancer. Surgery *146(5)*: 931-938, 2009.

141 Tischendorf JJ, Yagmur E, Scholten D, Vidacek D, Koch A, Winograd R, Gressner AM, Trautwein C, Wasmuth HE and Lammert F: The interleukin-6 (IL-6)-174 G/C promoter genotype is associated with the presence of septic shock and the ex vivo secretion of IL-6. Int J Immunogenet *34(6)*: 413-418, 2007.

142 Accardo Palumbo A, Forte GI, Pileri D, Vaccarino L, Conte F, D'Amelio L, Palmeri M, Triolo A, D'Arpa N, Scola L, Misiano G, Milano S and Lio D: Analysis of IL-6, IL-10 and IL-17 genetic polymorphisms as risk factors for sepsis development in burned patients. Burns *38(2)*: 208-213, 2012.

143 Gu W, Zeng L, Zhang LY, Jiang DP, Du DY, Hu P, Wang HY, Liu Q, Huang SN and Jiang JX: Association of interleukin 4 -589T/C polymorphism with Th1 and Th2 bias and sepsis in Chinese major trauma patients. J Trauma *71(6)*: 1583-1587, 2011.

144 Stanilova SA, Miteva LD, Karakolev ZT and Stefanov CS: Interleukin-10-1082 promoter polymorphism in association with cytokine production and sepsis susceptibility. Intensive Care Med *32(2)*: 260-266, 2006.

145 Arnalich F, Lopez-Maderuelo D, Codoceo R, Lopez J, Solis-Garrido LM, Capiscol C, Fernandez-Capitan C, Madero R and Montiel C: Interleukin-1 receptor antagonist gene polymorphism and mortality in patients with severe sepsis. Clin Exp Immunol *127(2)*: 331-336, 2002.

146 Dumon K, Rossbach C, Harms B, Gorelov V, Gross-Weege W, Schneider EM, Goretzki PE and Roher HD: Tumor necrosis factor-alpha (TNF-alpha) gene polymorphism in surgical intensive care patients with SIRS. Langenbecks Arch Chir Suppl Kongressbd *115(Suppl 1)*: 387-390, 1998, (in Germany).

147 Watanabe E, Zehnbauer BA, Oda S, Sato Y, Hirasawa H and Buchman TG: Tumor necrosis factor -308 polymorphism (rs1800629) is associated with mortality and ventilator duration in 1057 caucasian patients. Cytokine *60(1)*: 249-256, 2012.

148 Lee JH, Lee B, Lee HS, Bae EA, Lee H, Ahn YT, Lim KS, Huh CS and Kim DH: Lactobacillus suntoryeus inhibits pro-inflammatory cytokine expression and TLR-4-linked NF-kappaB activation in experimental colitis. Int J Colorectal Dis *24(2)*: 231-237, 2009.

149 Pino-Yanes M, Corrales A, Casula M, Blanco J, Muriel A, Espinosa E, Garcia-Bello M, Torres A, Ferrer M, Zavala E, Villar J and Flores C: Common variants of TLR1 associate with organ dysfunction and sustained pro-inflammatory responses during sepsis. PloS one *5(10)*: e13759, 2010.

150 Woehrle T, Du W, Goetz A, Hsu HY, Joos TO, Weiss M, Bauer U, Brueckner UB and Marion Schneider E: Pathogen specific cytokine release reveals an effect of TLR2 Arg753Gln during *Candida* sepsis in humans. Cytokine *41(3)*: 322-329, 2008.

Received July 16, 2013
Revised August 11, 2013
Accepted August 13, 2013