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# Induced Immunosuppression in Critical Care

*Evgeny Grigoryev, Vera Matveeva, Artem Ivkin  
and Maryam Khanova*

## Abstract

The maladaptive nature of the systemic inflammatory response syndrome, which may be caused by sepsis, trauma, or ischemia-reperfusion injury, is characterized by a shift towards the distant effects of pro- and anti-inflammatory mediators. Shock, blood loss, and metabolic disorders may cause the onset of multiple organ dysfunction syndrome. The final phase of critical illness is generally associated with induced immunosuppression and dysfunctions of neutrophils, monocytes and macrophages, dendritic cells, release of myeloid-derived suppressor cells, damage to glycocalyx and endothelium, and impaired metabolic conjugation. This review is aimed at providing novel evidences on the roles of various immune components, either innate or acquired, in the induction of immunosuppression from the standpoint of the rapid diagnosis of immune disorders in the intensive care unit using flow cytometry as a commonly accepted option.

**Keywords:** systemic inflammatory response syndrome, persistent multiple organ dysfunction, induced immunosuppression, flow cytometry

## 1. Introduction

Systemic inflammatory response syndrome (SIRS) refers to a critical illness, either infectious (sepsis) or secondary to tissue injury (tissue injury, cardiopulmonary bypass) that evolves into two phases. The first phase is an initial hyperinflammatory response, sometimes referred as a cytokine storm. Damage-associated molecular patterns (DAMP), also known as alarmins, and pathogen-associated molecular patterns (PAMP) activate the innate immune system. The activation of innate immunity is accompanied by a significant release of pro-inflammatory mediators that increase the intensity of the immune response and trigger adaptive immunity responses [1].

Excessive activation of pro-inflammatory mechanisms in SIRS patients drives the development of compensatory mechanisms to prevent excessive inflammation and weaken its excessive activity [2]. Negative feedback mechanisms downregulate this response in the first hours but may lead to the dysregulation and pathological over time, resulting in persistent suppression of immune response and increasing the risk of recurrent infections [3]. Numerous clinical and experimental trials on SIRS and sepsis have reported significant changes in the immunological profile, suggesting the phase of immune suppression to be the predominant immunological response in most patients after 7–14 days of persistent critical illness [4]. From the standpoint of critical care medicine, patients with sepsis cannot overcome the

primary bacterial infection even if they are actively treated, including antibacterial therapy. Patients with SIRS- and sepsis-induced immunosuppression acquire nosocomial and opportunistic infections contributing to the onset of multiple organ dysfunction syndrome [5].

The development of MODS is propagated by the dysregulation of the immune system. However, the interplay of pathophysiological mechanisms underlying the dysregulation of immune inflammatory processes is complex and requires in-depth studies. These mechanisms and their role are changing during the progression of the disease implying a heterogeneous immunological status specific to each patient. To date, researchers have focused on understanding the main changes in the innate and adaptive cellular immunity in critically ill patients, which may aid in the development of early and accurate individualized therapy protocols. Therefore, flow cytometry may be considered as a promising tool, enabling collecting highly accurate data at the preanalytical stage within a relatively short period of time. This review summarizes and discusses the most informative indicators of innate and adaptive cellular immunity in diagnosing and monitoring SIRS-induced immunosuppression.

## **2. Neutrophils**

Circulating numbers of neutrophils in blood are commonly increased by the rapid egress from the bone marrow and recruitment from the marginal pool to the circulating one.

Most studies have reported inconsistent alterations in the function of neutrophils in patients with sepsis at the early phase (impaired bacterial phagocytosis (activated or decreased, incomplete phagocytosis), increased synthesis of reactive oxygen species (ROS), decreased chemotaxis) [6]. Existing neutrophil dysfunction may be further aggravated or reversed. Therefore, impaired neutrophil function precludes insufficient bacterial clearance and neutrophil dysfunction and increases the susceptibility to infection [7]. It is worth noting that patients with severe neutrophil dysfunction are more prone to nosocomial and secondary infections [8]. Flow cytometry allows evaluating cell functional properties, but the interaction of external and internal factors (disease staging, blood sampling technique, sample storage, and preparation) should be taken into account before interpreting the obtained results.

Neutrophils are well-known highly informative predictors of adverse complications in patients with sepsis. Immature neutrophils with decreased expression of CD10 and CD16 (CD10-/CD16low) have exhibited an immunosuppression pattern implying the presence of the link with increased early mortality in patients with sepsis [9]. A unique CD10-/CD16low immature neutrophil subpopulation has been studied in cardiac patients. An increase in their concentration has been recorded even in the perioperative period. Thus, CD10-/CD16low neutrophils represent a significant portion of the circulating pool after cardiac surgery (over 40% of circulating neutrophils), emerge a left shift, and influence the phenotype and functional activity of circulating neutrophils [10].

## **3. Monocytes and macrophages**

Monocytes and macrophages play a pivotal role in triggering and regulating the immune responses [11]. Monocytes and macrophages are key players in the formation of the cytokine storm in the hyperactive phase of SIRS and sepsis. They are an important link with the onset and maintenance immunosuppression. Endotoxin tolerance is a well-known functional defect in monocytes and macrophages [12],

displaying a decrease in the release of pro-inflammatory cytokines in response to endotoxin (LPS) and other types of TLR stimuli [12]. Endotoxin tolerance may be induced in circulating monocytes as well as reticular spleen monocytes (splenocytes). It is directly related to immunosuppression, since a decrease in cytokine production blocks further expansion of the immune responses and limits the involvement of the cells of the adaptive immune system.

There are two *in vitro* assays evaluating the ability of monocytes to respond to the provocation of the immune system and detecting induced immunosuppression. The first includes the measurement of cytokines in cell culture supernatant in response to stimulation [13], whereas the second one assesses intracellular synthesis of cytokines. Fumeaux et al. have measured the level of production of intracellular cytokines and reported that monocytes in septic patients possess predominant anti-inflammatory phenotype with an increase in the intracellular ratio of IL10/TNF [14].

Main mechanisms implicated in the induction of monocyte and macrophage endotoxin tolerance in septic and sterile SIRS are considered as universal. Hyporeactivity has been repeatedly reported in septic patients, whereas endotoxin tolerance exhibited by monocytes has been first described in patients undergoing aortic surgery or those suffering from thermal trauma, hepatic/renal ischemia-reperfusion injury, coronary occlusion, and hemorrhagic shock [15]. However, the protective mechanisms of immunosuppression at the initial phase of hyperactivation of the immune response in patients with SIRS and sepsis may aggravate and lead to adverse events. In addition to endotoxin tolerance, anergy of monocytes and macrophages may be induced [16], capable to transit the last to an immunosuppressive state with the impaired antigen-presenting ability [17] and increased risk of nosocomial infections and adverse complications. The immunosuppressive phenotype of monocytes in SIRS and sepsis is characterized by a decrease in the expression of key MHC II genes and co-stimulating molecules (CD86, CD40, and HLA-DR), mediating a violation of antigen-presenting ability.

In addition, patients with sepsis-induced immunosuppression, as well as after cardioplegia during cardiac surgery, have demonstrated a significant decrease in the expression of the chemokine receptor CX3CR1 (receptor for fractalkine). Since the CX3CR1/CX3CL1 interaction mediates chemotaxis, adhesion, and migration of pro-inflammatory cells to the damaged area or infection, leading to tissue infiltration [18], its decreased expression on monocytes may prevent their migration with further phagocytosis and lesion sanitation.

Decreased cell surface expression of major histocompatibility complex class II (MHC II) is a key marker of suppressive functional rearrangement of monocytes. Indeed, low HLA-DR expression on monocytes has reported the correlation with lower synthesis of TNF- $\alpha$  and IL-1 in response to stimulation [19], decreased antigen-presenting ability [20], and expression level of the CD86 co-stimulatory molecule [21]. This biomarker is commonly used to monitor immunosuppression in various critical conditions. Clinical studies have reported that the magnitude and overtime persistence of HLA-DR reduction on monocytes correlates with an increase in mortality and the incidence of infections [22] associated with medical care provision in ICU patients [23]. It is worth noting that the monitoring of HLA-DR expression on monocytes during the first days after surgery does not allow predicting an increased risk of postoperative SIRS or sepsis or infectious complications in patients undergoing cardiac surgery.

Functional tests have confirmed the presence of the suppressor phenotypic transit in monocytes and have demonstrated lower proliferation of T-lymphocytes in the LPS-stimulated mixed culture of lymphocytes and monocytes in septic patients than healthy donor monocytes.

#### 4. Myeloid-derived suppressor cells (MDSC)

MDSCs are a heterogeneous population of immature myeloid cells with potent immunosuppressive activity against various types of cells, mainly T-lymphocytes. MDSCs have been first described in cancer patients as the cells capable to suppress the immune response, while orchestrating angiogenesis, invasion, and metastasis of tumors to the distant sites [24]. Certain difficulties have been experienced in comparing and interpreting data obtained in various research laboratories, caused mainly by the gap in the gating strategies and the description of the MDSC phenotype. In 2016, Bronte et al. published the recommendations for myeloid-derived suppressor cell nomenclature and characterization standards in 2016 and proposed to distinguish three main populations of MDSC: polymorphonuclear (PMN) or granulocytic MDSC (PMN-MDSC), monocytic MDSC (M-MDSC), and early-stage MDSC (eMDSC) [25].

The minimum set of the phenotypic criteria (but sufficient) to distinguish MDSC in humans is as follows:

M-MDSC: CD11b+CD14+HLA-DR<sup>low</sup>/<sup>-</sup>CD15-

PMN-MDSC: – CD14-CD11b+CD15+ or CD11b+CD14–CD66b+

eMDSC: Lin– (including CD3, CD14, CD15, CD19, CD56) HLA-DR–CD33+

M-MDSCs suppress both antigen-specific and non-specific T-cell responses associated with the production of NO and cytokines. PMN-MDSCs are capable of suppressing antigen-specific immune responses. The secretion of reactive oxygen species (ROS) by M-MDSC and PMN-MDSC is an important mechanism associated with the induction of the antigen-specific immune T-cell tolerance [26].

An early increase in MDSCs is associated with early mortality, while their persistent expansion with the prolonged length of stay in the ICU. Multivariate analysis has proved that a persistent increase in PMN-MDSCs appeared to be a strong independent predictor of nosocomial infections and poor prognosis [27], indicating the transition of the septic process to the induced immunosuppression. However, this transition is defined not only for sepsis, but also for other systemic inflammatory responses. Elevated levels of PMN-MDSC in patients at admission to the ICU is a strong predictor of mortality in the first 7 days. An increase in arginase in these patients directly correlates with the level of PMN-MDSC [28]. Various studies have shown a decrease in plasma concentrations of arginine in critical patients [29] with immunosuppression.

#### 5. Dendritic cells

Dendritic cells (DCs) are short-lived immune cells. Dendritic cell precursors originated from the bone marrow enter the bloodstream (circulating DCs) and then migrate to the tissues (tissue DCs), with most of the DCs being present in the tissues. DCs are antigen-presenting cells that induce T-cell immune responses, and the cytokines synthesized by DC activate innate and adaptive immunity [30].

Most of the studies are focused on the quantitative and qualitative assessment of DCs in patients with sepsis-induced immunosuppression, but few of them examines these processes in noninfectious SIRS. A decrease in the number of circulating DCs has been reported in patients with sepsis [31] and septic shock [32]. A significant decrease in the number of DC in spleens of septic patients who died has been found compared to trauma patients [33].

In systemic inflammatory response syndrome, DCs are well-known to be vulnerable to apoptosis. In addition, the induction of mDC and pDC apoptosis

promotes prolonged immunosuppression and persistence of infection [34]. The change of phenotype is closely associated with a decrease in the number of DCs. Thus, SIRS- and sepsis-induced immunosuppression are accompanied by a decrease in the antigen-presenting ability of DCs leading to reduced expression of HLA-DR, co-stimulatory molecules CD80/86, and transcription factor IRF4. It is worth noting that anti-inflammatory properties are activated in DCs, including increased synthesis of IL-10 and TGF $\beta$  [6]. Thus, the number of circulating DCs and the expression of HLA-DR may be a promising biomarker of SIRS- and sepsis-induced immunosuppression that requires further studies, including the use of flow cytometry.

## 6. Lymphopenia

Lymphopenia results in decreased resistance to pathogenic microorganisms and is considered as a non-specific yet commonly used marker of immunosuppression in critically ill patients [35]. If the adaptive immune system is weakened, the body has difficulties properly coordinating the fight against the pathogen leading to persistent primary or secondary infections. Depletion of each subpopulation of lymphocytes occurs (with the exception of regulatory T cells, see below) in the immunosuppressive phase of the disease. The degree of lymphopenia correlates with the development of health-associated infections and/or mortality within 28 days [36]. It is important to note that protracted lymphopenia in ICU patients is associated with the presence of infectious complications [37], and this indicator is a better predictor of bacteremia than C-reactive protein and white blood cell count.

## 7. NK cells, $\gamma\delta$ -lymphocytes, mucosal-associated invariant T-lymphocytes

Flow cytometry have reported a significant decrease in the number of circulating NK cells in patients with severe trauma and sepsis. A long-term decrease in NK cells correlates with an increase in mortality [38]. In addition, a decrease in cytotoxicity and antibody-dependent cytotoxicity of NK cells during sepsis have been previously reported [39].

Septic patients also have a decrease in circulating mucosal-associated invariant T-lymphocytes (MAIT) [40], while a persistent decrease in MAIT correlates with the subsequent development of health-associated infections.

A significant decrease in the relative content of  $\gamma\delta$ -lymphocytes has been found in patients with sepsis with prevailing non-proliferating  $\gamma\delta$ -lymphocyte population [41].

## 8. T-lymphocytes

### 8.1 Quantitative changes in T-lymphocytes

Quantitative and functional changes in T-lymphocytes occur in patients with induced immunosuppression. They include activation of apoptosis, anergy, and depletion, an increase in the percentage of Treg cells. Each of these changes will be considered separately.

One of the causes of lymphopenia in immunosuppression is associated with the death of T and B lymphocytes through apoptosis. There are a lot of evidences

confirming a decrease in the number of circulating and deep depletion of tissue resident CD4 + and CD8 + T-lymphocytes during sepsis [42].

## **8.2 Programmed cell death receptor 1 (PD-1) and its ligand (PD-L1)**

An important mechanism for enhancing apoptotic cell death is associated with increased expression of the programmed cell death receptor 1 (PD-1) and its ligand (PD-L1). PD-1 is a negative co-inhibitory molecule expressed by lymphocytes, myeloid cells, and DC. Under physiological conditions, PD-1 is associated with negative regulation of the immune system by preventing the activation of T-lymphocytes, which reduces autoimmunity and increases self-tolerance. The inhibitory effect of PD-1 is through stimulation of apoptosis of antigen-specific T-lymphocytes in the lymph nodes and a decrease in apoptosis of regulatory T-lymphocytes (Treg). The main PD-1 ligand (PD-L1) expresses epithelial cells, endothelial cells, and antigen-presenting cells (APCs) [43]. Flow cytometry reported that the expression of PD-1 on T-lymphocytes and PD-L1 on monocytes drastically increased in patients with septic shock and led to accelerated apoptosis of all major lymphocyte subpopulations compared to healthy volunteers [44]. Macrophages also express higher PD-1 levels during sepsis, which is associated with dysfunction of these cells and a decrease in microbial clearance [45].

Excess expression of PD-1 and PD-L1 on immune cells leads to their deactivation and acceleration of apoptotic death, resulting in the formation and development of sepsis- and SIRS-induced immunosuppression [46]. Day et al. have found an increase in the expression of PD-1 and PD-L1 on CD4 + T-lymphocytes within the first 5 days of hospitalization in patients with sepsis and severe trauma compared with healthy donors. The expression level of PD-1 and PD-L1 correlated with a decrease in stimulated proliferative lymphocyte activity and an increase in the concentration of IL-10 (anti-inflammatory cytokine) in the blood [47].

In addition to the direct apoptotic effects of PD-1 and PD-L1 molecules on T-lymphocytes, they indirectly affect the number of antigen-presenting DCs. Antigen-presenting cells (APC) activate CD4+ T-lymphocytes, which quickly proliferate (clonal expansion is a feature common to all adaptive immune responses) and differentiate into different effector lines, namely, Th1, Th2, and Th17. The decrease in the number of DCs suppresses clonal expansion along with the direct apoptotic effects of PD-1/PD-L1, which may lead to a pronounced decrease in the number of B- and T-lymphocytes [33].

Experimental and clinical trials have proved the pivotal role of PD-1 and PD-L1 in the pathogenesis of induced immunosuppression. The correlation of the expression of these molecules on the surfaces of immune cells with the development of infectious complications and an unfavorable outcome has been determined. Thus, a high level of PD-L1 expression on neutrophils correlates with an increase in the blood levels of pro- and anti-inflammatory cytokines and an unfavorable outcome in septic patients [48]. A relationship between the increased expression of PD-1 on monocytes in patients with septic shock and mortality and the risk of secondary nosocomial infections has been recently reported. Similarly, an increase in PD-1 and PD-L1 by Th also correlates with an increase in the number of secondary nosocomial infections and mortality after septic shock and severe trauma [49].

## **8.3 Qualitative changes in T-lymphocytes**

In addition to a quantitative decrease in CD4 + T-lymphocytes, there is a simultaneous decrease in cytokine production and a decrease in the main transcription factors in the Th1 and Th2 populations (T-bet for Th1 cells, GATA3 for Th2 cells) in

patients with sepsis [50]. These processes are associated with anergy and depletion of T-lymphocytes. The concept of depletion was introduced by Zajac to describe the impaired effector function of T cells [51]. Dysregulation of T-cell functions has been previously reported in patients with neonatal and pediatric sepsis and ICU patients with hemorrhagic shock and severe tissue damage followed by induced immunosuppression [52].

#### **8.4 An increase in the relative number of Treg**

T-lymphocyte dysfunction, if immunosuppression has induced, is associated with an increase in the relative number of circulating Treg lymphocyte subsets (T-cells with regulatory properties). Originally, this phenomenon was described in patients with septic shock [53]. Treg functions mainly at the site of inflammation, modulating the immune response via three main mechanisms: direct killing of cytotoxic cells, inhibition of cytokine production by cytotoxic cells, and direct secretion of immunomodulating anti-inflammatory cytokines, such as TGF- $\beta$  and IL-10 [54]. An increase in Treg levels has been previously observed immediately after the shock but has persisted only in patients with unfavorable outcomes. One of the mechanisms includes Treg cells resistance to sepsis-induced apoptosis compared to other T-cell populations. Blood levels of Treg cells in ICU patients can be considered as a prognostic marker for the development of septic complications and adverse outcomes [55].

Thus, the relative number of Treg cells and the level of expression of CD39 on Treg cells require further detailed study that may provide novel insights into the diagnosis of SIRS- and sepsis-induced immunosuppression. However, accurate results of any multicenter study require standardization of Treg phenotyping approaches, since various staining protocols and gating strategies are used (CD4 + CD25 +, CD4 + CD25 + CD127-, CD4 + FOXP3 +, etc.).

#### **8.5 B- and T-lymphocyte attenuator (BTLA) and cytotoxic T-lymphocyte antigen-4 (CTCTLA-4)**

T-lymphocyte dysfunction can contribute to the induction of immunosuppression and subsequent mortality. BTLA and its ligand express a wide variety of cells, including T and B lymphocytes. BTLA is a co-inhibiting receptor that inhibits CD4 + T-cell and B-cell functions and also suppresses signaling in CD4 + T cells aimed at their survival. The relative number of BTLA +/CD4 + lymphocytes was significantly higher in septic patients than in non-septic ICU patients and was associated with the subsequent onset of secondary infections. CTLA-4, if interacting with CD80 or CD86, may be regarded as other inhibitory regulator in the early stages of T-cell activation and proliferation. CTLA-4 is an important inhibitor of the functional activity of immune cells, and its expression is increased in patients with sepsis [56].

### **9. Conclusion**

The review proves that there are similar mechanisms underlying the induction of immunosuppression in septic and sterile systemic inflammatory processes and justifying the use of the term “injury-induced immunosuppression.” Immunological monitoring will allow distinguishing between the rapidly changing phases of progressive inflammation and severe immunosuppression to optimize early diagnosis and treatment (**Table 1**).

Marker	Status	Diagnostic significance or the underlying mechanism triggering immunosuppression	Prognostic value
% CD10-/CD16low out of the total concentration of neutrophils	↑	Immunosuppression	Sepsis-associated mortality
% CD62L dim out of the total concentration of neutrophils	↑	Immunosuppression	–
CD86 expression on monocytes	↓	Decrease in antigen-presenting function	Long-term decrease combined with a decrease in HLA-DR. Increased mortality and healthcare-associated infections
HLA-DR expression on monocytes or levels of M-MDSC	↓ ↑	Decrease in antigen-presenting function	Increased mortality and healthcare-associated infections
CX3CR1 expression on monocytes	↓	Reduction in monocyte chemotaxis	Increased mortality
PMN-MDSC	↑	T-cell-mediated suppression	Increased mortality and healthcare-associated infections
Blood levels of DCs	↓	Immunosuppression	Increased mortality and healthcare-associated infections
HLA-DR expression on DCs	↓	Decrease in antigen-presenting function	Increased mortality and healthcare-associated infections
Lymphopenia	↓	Immunosuppression	Increased mortality and healthcare-associated infections
PD1 expression on T-lymphocytes	↑	Enhanced apoptosis of T-lymphocytes	Increased mortality and healthcare-associated infections
PD-L1 expression on monocytes	↑	Enhanced apoptosis of all lymphocyte subpopulations	Increased mortality and healthcare-associated infections
Relative blood levels of Treg cells	↑	Immunosuppression	Increased mortality and healthcare-associated infections
CD39+ expression on Treg cells	↑	Immunosuppression	Differential diagnosis of sepsis and SIRS and increased mortality
BTLA and CTLA-4 expression on lymphocytes	↑	Suppression of lymphocyte activation and proliferation	–

**Table 1.** Diagnostic and/or prognostic values of the main immunological parameters of flow cytometry associated with injury-induced immunosuppression in ICU patients.

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### **Author details**

Evgeny Grigoryev\*, Vera Matveeva, Artem Ivkin and Maryam Khanova  
Scientific Research Institute for Complex Issues of Cardiovascular Diseases,  
Kemerovo, Russian Federation

\*Address all correspondence to: [grigev@kemcardio.ru](mailto:grigev@kemcardio.ru)

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