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# Monitoring the Immune System in Critically Ill Patients (Review)

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## Summary

Most patients with critical illness, regardless of the cause, develop activation of innate and adaptive immunity. This is often a critical process leading to organ dysfunction.

**The aim of the review** is to systematize information on monitoring the immune system in critical illness for physicians of different specialties (anesthesiology and intensive care, surgery, general practice, obstetrics and gynecology).

The review includes information from 83 recent national and international publications (mostly from 2023), available in the public domain and found by keyword search.

We have summarized the current understanding of the relationship between infections and the human immune system, as well as the clinical application of traditional markers of immune status. We provided data on novel promising markers for the assessment of immunity in patients with various diseases.

Limitations of the studies reviewed include the need for additional large-scale clinical trials of even the most promising markers, as well as a synthesis of the evidence for their performance. In addition, immune monitoring is likely to increase the cost of patient care, necessitating the development of more affordable research methods.

**Conclusion.** Almost all disorders in critically ill patients are associated with changes in the immune system. Management of patients based on their immune profile requires determination of a personalized strategy for immune modulation, treatment, and prevention of infection. Advanced monitoring of immune system functions will contribute to the personalization of medicine, and the continuous development of biological technologies will allow to improve its methods.

***Keywords: immune system monitoring; critical illness; biomarkers; immunity; sepsis; multiple organ failure***

**Conflict of interest.** The authors declare no conflict of interest.

## Introduction

The status of the immune system is pivotal in critical illness. Whether caused by infection, trauma, or other tissue damage, most patients admitted to the intensive care unit (ICU) have an overactivation of innate and adaptive immunity. This has a vital importance and can often lead to organ dysfunction. In addition, therapeutic interventions aimed at restoring homeostasis can also alter the course of chronic diseases and promote their progression.

Secondary infections are the most common manifestation of immune system dysfunction. They are the leading cause of mortality in intensive care units worldwide and their treatment is associated with significant financial costs [1, 2].

The pathogenesis of severe infections is characterized by an uncontrolled immune response leading to excessive release of inflammatory mediators and developing immune dysfunction, which may persist for a long time even after treatment is completed [3].

In recent years, researchers have focused on infection-induced immune dysregulation due to its role in the development and prognosis of sepsis [4, 5]. Consequently, the identification of biomarkers for monitoring the immune status may provide valuable information for early diagnosis, effective prevention, and treatment of septic complications. However, despite extensive research in recent years, in-depth monitoring of the immune system in critically ill patients has not become routine.

Severe tissue and organ damage is a hallmark of critical illness. While intensivists are well-versed in monitoring the brain, heart, lungs, gastrointestinal tract, and kidneys, they are less familiar with immune monitoring and its implications for assessing immune function.

Aim of the review. To systematize information on immune system monitoring in critical illness for physicians of different specialties (anesthesiologists, intensivists, surgeons, general practitioners, obstetricians and gynecologists).

## Immune Status and Infections

Immune dysfunction plays a central role in the development of sepsis complications. Pattern recognition receptors (PRRs) directly identify molecular structures on the surface of pathogens,

apoptotic host cells and damaged senescent cells. Through recognition and binding, PRRs exert non-specific anti-infective and other immunoprotective effects. Immune cells recognize pathogen-associated molecules (PAMPs) and damage-associated molecules (DAMPs) through PRRs. PAMPs are specific and highly conserved molecular structures that are unique to specific pathogens. PAMPs are essential for pathogen survival and often possess unique molecular or subcellular properties not found in host cells. Cells of the innate immune system can recognize PAMPs through PRR, distinguish between «self» and «foreign», and respond to pathogens and their products. PRR can also recognize DAMP and activate innate immunity. Binding of PRR to PAMP or DAMP leads directly to phagocytosis of pathogens by immune cells. The inflammatory response enhances the ability of the body to destroy invading pathogens. Immune cells such as natural killer cells, macrophages, dendritic cells, and parenchymal cells, both epithelial and endothelial, are involved in the early local immune response to pathogens. The interaction of PAMP and PRR activates these cells, triggering intracellular signaling pathways that involve key factors and regulate the inflammatory response [6, 7].

In most cases, the immune system effectively eliminates invading pathogens through a combination of proinflammatory responses and repair mechanisms. The proinflammatory response aims to destroy pathogens through the release of cytokines and chemokines, recruitment of phagocytes, and local activation of the complement and coagulation systems. Simultaneously, this anti-inflammatory mechanism restores homeostasis. However, in severe sepsis, the immune system cannot destroy pathogens because the dynamic balance and regulation of physiological processes are disrupted, leading to excessive inflammation and immunosuppression. The severity of immune dysfunction varies widely among individuals [8].

Sepsis manifests as a complex state of immune dysfunction, characterized by a constant release of inflammatory mediators. The characteristic inflammatory response to infection is the activation of the vascular endothelium, complement, coagulation system, and neutrophil extracellular traps. Endothelial dysfunction is present, as is the activation of platelets and B cells, both of which have closely related and cross-regulated functions. Persistent immune stimulation in severe sepsis is attributed not only to pathogen entry but also to the release of DAMPs, which activate PRRs. These PRRs often recognize PAMPs and initiate a deleterious cycle of sustained immune activation and dysfunction. Systemic activation of the innate immune system by PAMP and DAMP causes a severe and sustained inflammatory response, commonly referred to as the «cytokine storm» characterized by the excessive release of inflammatory cytokines such as IL-1, TNF, and IL-17 [9, 10].

The excessive inflammatory response leads to cell and tissue damage, molecular dysregulation, and ultimately organ dysfunction, including multiple organ failure. Sepsis patients who survive the initial hyperinflammatory phase enter the subsequent immunosuppressive phase. The relationship between hyperinflammation and immunosuppression is complex and, contrary to previous beliefs, they do not always occur sequentially. Immunosuppression can coexist with excessive inflammation, particularly in viral infections, characterized by lymphocyte depletion and reprogramming of antigen presenting cells (APCs) [11, 12].

The immunosuppression seen in sepsis is closely associated with significant depletion of key immune cell populations, including CD4+ and CD8+ T cells, dendritic cells (DCs), and B cells. The loss of lymphocytes significantly impairs the ability of the immune system to effectively fight and destroy pathogens [13, 14].

Sepsis causes delayed neutrophil apoptosis (which correlates with the severity of the disease) and a rapid increase in neutrophil levels. Although neutrophil apoptosis is delayed, accelerated apoptosis of other immune cells can compromise the host immune system by inducing dephosphorylation of epithelial caspase-8. As systemic inflammation progresses, persistent neutrophil dysfunction combined with the release of immature neutrophils eventually leads to neutrophil deficiency [15, 16].

Apoptosis-induced reduction in the number and function of DCs, which are highly efficient APCs, can lead to impaired innate and adaptive immune responses. This includes downregulation of HLA-DR expression, induction of tolerance to endotoxin, and decreased cytokine production, all of which impair the ability of APCs to stimulate lymphocytes and drive immune function. Thus, apoptosis exacerbates sepsis-induced immunosuppression of both the innate and adaptive immune systems. Therefore, exploring potential therapeutic targets to inhibit immune cell apoptosis holds great promise for reversing sepsis-induced immunosuppression [17–19].

Another phenomenon that exacerbates the patient's condition is immune cell autophagy. It is observed in almost all cell types involved in adaptive immunity, such as lymphocytes, APCs and myeloid cells. Autophagy is an important mechanism for killing intracellular bacteria that affect T and B cells. The effect of immune cell autophagy on the body is a complex process, and when immune cells can initiate programmed death, it reduces inflammation in the body. However, if autophagy is excessively enhanced, the harmful effects may outweigh the protective effects [20, 21].

**Table. Immune status markers presented in the review.**

| Markers of immune status | |
|---|---|
| **Traditional** | **Promising** |
| Leucocyte differential | Neutrophil function markers: CD64, CD88, CD64, TREM-1, NET |
| C-reactive protein | HLA-DR expression |
| Procalcitonin | Myeloid-derived suppressor cells (MDSC) |
| Cytokines and chemokines | Dendritic cell assay |
| | Complex analysis of T and B lymphocytes |
| | Immune checkpoint analysis: PD-1 and PD-L1, Tim-3, CTLA-4, LAG-3, BTLA |
| | Analysis of changes in apoptosis and autophagy of immune cells |

The ability to fight infection is also influenced by the characteristics of the patient's epigenome. Post-translational histone modifications and DNA methylation have been shown to alter the phenotype of immune cells [22, 23].

## New Information About Traditional Markers of Immune Status

Inflammatory response is currently monitored using all-purpose tests that do not distinguish between the type of response or the etiology of the inflammation (Table).

The leukocyte formula is the most commonly used test to assess the immune system response and is often underestimated. After activation of the acute inflammatory response and release of adrenaline, the residence time of leukocytes in the lung or spleen decreases, contributing to a rapid increase in their number in the blood. This response is brief and nonspecific for infection, but is a sensitive marker of the inflammatory response.

In addition to absolute and relative neutrophil counts, the prognostic value of the neutrophil-to-lymphocyte ratio has been demonstrated in many studies and can be incorporated into clinical practice. In fact, neutrophil elevation is usually associated with a sharp decrease in lymphocyte count and increased mortality during critical illness [24–26]. There are potentially many reasons for such lymphopenia, such as increased apoptosis following a rapid increase in the concentration of proinflammatory cytokines, massive lymphocyte migration into tissues, decreased lymphopoiesis as an acute response to pathogenic stimuli, but the unifying pathophysiologic mechanism combining all of these factors has not yet been described.

Soluble markers such as C-reactive protein (CRP) and procalcitonin are used for bedside monitoring and clinical decision making. However, their role in the immune response is often overlooked.

CRP is mainly produced in the liver, but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes and adipocytes in response to IL-6 release. Thus, in any clinical situation with a high concentration of IL-6, there may also be a high concentration of CRP circulating in the bloodstream. CRP binds to complement molecules and, depending on the form in which it is presented (monomeric or pentameric), contributes to the opsonization of microorganisms, activation of neutrophils and monocytes, and stimulation or inhibition of the inflammatory response [27, 28].

Most infectious diseases induce a generalized immune response, so the diagnostic value of CRP is low and its use is not recommended when deciding on the use of antibiotics. On the contrary, monitoring of CRP may be useful to assess the response to pathologic agents. In patients with community-acquired or nosocomial pneumonia, a halving of the CRP level 72 hours after the start of antibiotic therapy was associated with a better prognosis and an effective response to antimicrobial therapy. On the other hand, it should be emphasized that the existing studies are very heterogeneous, some of them have methodological gaps, which does not allow drawing unequivocal conclusions on this topic [29, 30].

Procalcitonin is a molecule produced both by the parathyroid gland and by adipose tissue. In the former, its secretion is dependent on calcium and vitamin D levels, while in the latter it is released as procalcitonin in response to inflammatory stimuli such as IL-1 or IL-6. The expression of procalcitonin in adipose tissue is inhibited by IFNγ (a major cytokine involved in the antiviral response) and IL-17, which is actively released during infection. Procalcitonin should be more widely used as a test to monitor the patient's response to treatment and promote earlier discontinuation of antibiotic therapy [31, 32].

A recent meta-analysis evaluating 99 biomarkers in 15,681 patients showed that initial measurement of procalcitonin, CRP, IL-6 and sCD14 alone did not help predict mortality in critically ill patients with sepsis [33].

Thus, none of the reported soluble markers help to determine the severity of immune dysfunction and do not reflect the overall response of the host organism to infection.

In this regard, quantification of cytokines and chemokines may be more accurate in determining the nature of the immune response. Measurement of serum cytokines has provided endotypes for many manifestations of critical illness in ARDS or sepsis [34, 35].

The increasing availability of assays for the measurement of these molecules may in the future help to integrate them into clinical decision protocols

for the diagnosis of infection and immune dysfunction. Some serum cytokines are already used as markers in clinical practice. In critically ill patients, measurement of IL-6 levels was used during the pandemic and helped to determine the indication for tocilizumab [36].

Cytokine levels are thought to be associated with the development and severity of sepsis and are therefore reliable biomarkers. Examples include pro-inflammatory cytokines such as interferon-β (IFN-β) and interleukins (IL-1β, IL-3, IL-6, and IL-7) [37].

A recent meta-analysis included 145 studies reporting 26 immunological, 11 hematological, 5 inflammatory, 4 coagulation and 10 biochemical parameters. Cytokines (IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-$\alpha$, IFN-γ, IgA, IgG) and CD4+ T/CD8, CRP, ferritin, D-dimer, serum amyloid protein A and LDH were measured. These parameters were significantly elevated in critically ill patients or in those who did not survive. In addition, patients who were not critically ill or survivors had significantly higher counts of lymphocytes, monocytes, eosinophils, CD3+ T, CD4+ T and CD8+ T cells, B cells and NK cells, as well as the lymphocyte/monocyte ratio. Disruption of innate and adaptive immune responses, as reflected by decreased levels of eosinophils, lymphocytes, monocytes, B cells, NK cells, T cells, and CD4+ and CD8+ T cell subtypes, as well as impaired blood coagulation and lung damage, were characteristic of patients with poor prognosis [38].

This is also proved by the studies of Russian researchers. Postoperative inflammatory stress response was evaluated by changes in CRP, IL-1β, IL-6. There was a correlation between the level of proinflammatory cytokines and the severity of pain [39]. Levels of systemic inflammatory response markers (IL-6, CRP) did not affect survival and length of hospital stay. Hemoperfusion in patients with severe COVID-19 provided a decrease in CRP concentration on the 1st day after administration. When started early, it promoted a significant increase in survival and shortened the duration of treatment [40]. Cytokine profiles of activated B lymphocytes and their subpopulations were determined. The results show that cytokine production by B cells is significantly dependent on the activation and differentiation of B lymphocytes [41]. A number of cytokines (IL-25, IL-33 and TSLP) are involved in the mechanism of development of allergic diseases [42]. The obtained data on changes in the levels of cytokines of the IL-10 family and IFN type III demonstrate a disturbed interaction between the systems of innate and adaptive immunity in inflammatory skin diseases with early subclinical development of severe inflammatory response [43]. The above works partially describe the alterations in immunity, but a complete picture of the immune status is still missing.

## The Most Promising Markers Associated with Immune Cells

The assessment of the inflammatory response is certainly incomplete if it is based only on soluble markers and does not take into account the cellular phenotype and the expression of biomarkers in cells. These indicators reflect specific immune changes and contribute to a better characterization of the immune profile (Table).

**Monitoring neutrophil function.** Decreased neutrophil bactericidal activity correlates with the severity of sepsis-induced immunosuppression, particularly in patients with poor prognosis. Common markers of neutrophil function include CD64, triggering receptor expressed on myeloid cells (TREM-1), and CD88 [44, 45]. CD64 and TREM-1 are neutrophil proteins whose activation affects neutrophil function. Decreased expression of CD88 on neutrophils is closely associated with an increased incidence of subsequent secondary infections and is a strong predictor of immunosuppression [46]. Neutrophils produce extracellular traps (NETs) to capture pathogens. NETs are involved in the inflammatory response, killing and clearance of bacteria. However, their overactivation can lead to an «inflammatory storm» and damage to tissues and organs [47].

**Monitoring monocyte/macrophage function.** Monocytes are antigen-presenting cells that modulate adaptive and innate immunity and influence the nature of the T-cell response. Antigen presentation depends on the number of HLA-DR molecules. HLA-DR expression is a reliable marker of the antigen presenting capacity of monocytes. Poor recovery of mHLA-DR may serve as an early guide for clinicians in assessing the prognosis of patients with sepsis [48]. Reduced risk of reinfection correlates with increased mHLA-DR expression in peripheral blood monocytes of such patients [49]. Periodic monitoring of mHLA-DR expression together with CRP may help to identify patients at increased risk of sepsis in the ICU [50].

**Monitoring the function of myeloid-derived suppressor cells.** MDSCs were first discovered in cancer patients and mice. They significantly reduce anti-tumor immunity mediated by T and NK cells. Inflammation is a common feature of many diseases and normal physiological conditions and is the primary driver of MDSC accumulation and function. Although MDSCs are detrimental in cancer, they can be beneficial in situations where cellular immunity is overactive. Because MDSCs can be generated ex vivo, they may be employed as therapeutic agents to mitigate the damage caused by overactivated cellular immunity. MDSCs play an important role in the inhibition of innate and adaptive immune responses, including the immune responses in sepsis. MDSCs have been found to be consistently high in sepsis patients and elevated in nosocomial infections [51].

**Monitoring NK cell function.** The involvement of macrophages, neutrophils and DCs in the development of sepsis has been confirmed, but the role of natural killer cells (NK cells) is still unclear. On the one hand, activation of NK cells is thought to increase the risk of severe organ damage or death. However, other studies have found that activation of NK cells improves the course of sepsis [52]. The relationship between CD8+ T cells and 28-day mortality in sepsis is dependent on the number of NK cells [53]. Tim-3 expression is strongly correlated with NK cell function. Increased Tim-3 expression promotes NKT cell activation and apoptosis in the early stages of sepsis, which is associated with increased disease severity and poorer prognosis. Blocking the Tim-3/galectin-9 signaling axis with $\alpha$-lactose prevents in vitro apoptosis of NKT cells isolated from sepsis patients. Disruption of Tim-3 activity protects mice against septic infection [54].

NK cells exert cytotoxic effects through the production of various cytokines, the most typical of which is IFN-γ. Serum levels of IFN-γ are an indicator of NK cell function [55].

**Analysis of dendritic cells (DCs).** DCs are important APCs that play a critical role in the regulation of both innate and acquired immune responses. In sepsis, the number of DCs decreases with inhibition of antigen-presenting capacity and is accompanied by abnormal cytokine secretion, resulting in impaired T lymphocyte activation. DC depletion and dysfunction are the major causes of the development of immunosuppression associated with sepsis. Based on the characteristic changes of DCs in sepsis, a novel immunomodulatory strategy targeting apoptosis, differentiation, and dysfunction of DCs has been proposed for the prevention and treatment of severe burns and trauma complicated by sepsis [56]. Activation of cannabinoid receptor 2 in acute lung injury associated with sepsis may improve disease outcome by modulating DC maturation [57]. PTEN-induced kinase 1 (dual substrate specificity phosphatase, PTEN gene product) protects against DC dysfunction during sepsis by regulating mitochondrial function control [58]. IL-3 enhances antiviral immunity by improving the recruitment and function of circulating DCs [59]. T. Zhang et al. identified novel anergic DC subtypes characterized by low major histocompatibility complex class II expression in a subset of patients studied [60]. These anergic DC subtypes were significantly more frequent in patients with sepsis.

Sepsis severity correlated with overexpression of programmed death ligand 1 on antigen-presenting cells. Combined analysis of SOFA or APACHE II scores and programmed death ligand 1 levels in monocytes and DCs may improve the quality of mortality prognosis [61]. Cell wall peptidoglycan released during bacterial replication activates human DCs as evidenced by increased expression of surface HLA-DR, CD83, T cell costimulatory molecules CD40 and CD86, and chemokine receptor CCR7. Cell wall peptidoglycan increased the production of IL-23, IL-6 and IL-1β. DCs stimulated by cell wall peptidoglycan induced differentiation of allogeneic CD4+ T cells into T helper cells producing IL-17 and IL-21 [62]. Hemorrhagic shock, through impaired DC function and maturation, inhibited cytokine production, playing an important role in immunosuppression [63].

**T Lymphocytes.** Monitoring cytokine production is a key measure of T cell function and differentiation. Lymphopenia is a common feature of acute inflammation [64]. Although the underlying mechanisms are not fully understood, the involvement of IL-7 is likely. IL-7 and CD127 receptor activity is associated with mortality. This activity is particularly reduced in septic shock [65].

In addition to normalizing T cell counts, maintaining a diverse repertoire of T cells and a quantitative balance between each cell phenotype is critical for full recovery of homeostasis. During post-traumatic sepsis, the T cell response «shifts» toward the TH2 phenotype, resulting in the loss of TH1. The TH17/Treg ratio has a very strong positive correlation with the SOFA score, indicating that the higher the ratio, the worse the patient's prognosis [66].

Another study looked at 2570 patients with sepsis from 25 studies. Cytokine levels were measured in the ICU before and after treatment. A meta-analysis found that a decrease in IL-6 and TNF-$\alpha$ levels after sepsis treatment may indicate a better prognosis and survival in patients [67]. Cytokines can play both pro- and anti-inflammatory roles. Complex interactions between cytokines, vascular cells, and immune cells lead to a «cytokine storm» and multiple organ failure, all of which contribute to the severity of the patient's condition [68].

According to the pathobiology of sepsis, biomarkers can be classified into 4 pathophysiological groups related to immune dysregulation, endothelial damage and coagulopathy, cellular damage, and organ damage. However, large and multicenter studies confirming the reliability of routine use of circulating proteins for diagnosis or prognosis in sepsis are lacking [69].

**B lymphocytes.** Serum IgG, IgA, and IgM concentrations directly reflect B cell status and activity [70]. Septic shock is associated with B-lymphocyte deficiency and lymphopenia. Most studies have focused on the changes in a number of immune cells during sepsis, while ignoring B cells. It turns out that B cells play a more important role in sepsis than previously thought. Both pathogen clearance and survival were reduced in B-cell-deficient mice with sepsis, whereas additional B cells improved survival in Rag1-deficient mice. Upon encountering

antigen, B cells differentiate into antibody-secreting cells and memory B cells. Most studies report a depletion of circulating B cells in patients with sepsis and a poor prognosis. Their overall depletion may be related to impaired apoptosis and maturation. Sepsis also impairs B cell function [71, 72].

In addition to decreased B cell counts, patients with sepsis develop significant B cell dysfunction. Increased expression of CD80 and CD95 on the surface of B lymphocytes is associated with an increased risk of death in patients with sepsis [73, 74].

**Effects on immune checkpoints.** The checkpoints are located on the surface of various cells and may reflect immune status. The most studied are the PD-1 (programmed cell death-1) protein and the programmed cell death ligand 1 (PD-L1). Studies have shown that PD-1 and PD-L1 are closely associated with cancer progression in humans and are promising therapeutic targets. In addition, the interaction between PD-1 and PD-L1 is one of the mechanisms by which human tumor cells evade the immune response. Several drugs targeting checkpoint inhibitors, including PD-1 and PD-L1, have been developed and approved for the treatment of various cancers [75]. Preclinical studies of targeted immunosuppression, particularly with immune checkpoint inhibitors, have demonstrated reversal of immune cell dysfunction and development of host resistance to infection [76]. PD-1 inhibition with nivolumab is a promising treatment option for immunosuppressed patients. It reactivates T lymphocyte function and restores immunity to fight infection [77].

Other immune «checkpoint» molecules of interest include cytotoxic T-lymphocyte antigen-4 (CTLA-4), T-cell membrane-3 (TIM-3), lymphocyte activation gene 3 (LAG-3), and B- and T-lymphocyte attenuator (BTLA) receptor.

Cytotoxic CTLA-4 is an immune control molecule expressed mainly on activated T cells and regulatory T cells (Treg), which inhibits T cell activation and regulates immune homeostasis. Based on the crucial functions of CTLA-4 in T cell biology, immunotherapies targeting CTLA-4 have been developed for the treatment of autoimmune diseases and cancer [78].

TIM-3 has been identified on the surface of T helper 1 (Th1) cells, cytotoxic lymphocytes, monocytes, macrophages, natural killer cells and dendritic cells. TIM-3 plays a key role in immune regulation. The inhibitory checkpoint TIM-3 is expressed on the cell surface in most cancers, chronic autoimmune diseases, inflammatory gastrointestinal diseases, and some viral and parasitic diseases [79].

LAG-3 (CD223) has a regulatory role similar to PD-L1 and CTLA-4, which is to inhibit immune function, cell proliferation, maintain homeostasis and cytokine production. LAG-3 is expressed on Treg cells, natural killer cells, invariant NK-T cells, activated CD4+ T helper and cytotoxic CD8+ T lymphocytes, B cells and plasmacytoid dendritic cells after antigen stimulation. High expression of LAG-3 was found in a variety of tumors. Its expression was mainly associated with poor outcomes, including tumor progression, treatment resistance and metastasis. The identified associations provide a rationale for the measurement of novel biomarkers [80].

The recent introduction of monoclonal antibodies targeting immune «checkpoints» for antitumor immunity has revolutionized the treatment of tumors. The success of therapies based on immune checkpoint blockade depends mainly on blockade of PD-1/PD-L1 and CTLA-4. However, the lack of reliable prognostic biomarkers with limited overall patient response is a major factor hindering the success of immunotherapy. BTLA may be a novel target for cancer immunotherapy. Disruption of BTLA upregulation is common and associated with poor prognosis in solid and hematological malignancies. Binding of the BTLA receptor to the herpes virus entry mediator (HVEM) ligand on the surface of T cells results in decreased cell activation, cytokine production, and proliferation [81].

In recent years, significant progress has been made in the development of approaches that focus primarily on immunotherapy, aiming to block molecules involved in immune evasion. However, there are still problems in predicting their efficacy due to the great heterogeneity of clinical responses. Thus, there is a need to develop new strategies, both in cancer and in other diseases [82].

Preclinical and early clinical studies have shown that levels of PD-1, PD-L1, CTLA-4, TIM-3, LAG-3 and BTLA cytotoxic antigens are increased on immune cells in sepsis. This is thought to be a major contributor to immune cell dysfunction. These inhibitory regulators interfere with the immune responses needed to destroy invading pathogens. Their interaction with various immune cells has been shown to inhibit innate immune functions (e. g., phagocytosis, cytokine production, and pathogen clearance) and also results in impaired T cell competence [83].

Analysis of epigenetic features [22, 23], alterations in apoptosis [17–19] and autophagy of immune cells [20, 21] are of great importance in assessing the overall picture of immune system disorders.

Currently, multiple variables are used in the ICU to assess the efficacy of hemodynamic stabilization. As a result, it is likely that more than one marker will be required to identify a reliable endotype representing immune function.

## Conclusion

Almost all disorders in critically ill patients lead to alterations in immune status. Detailed mon-

itoring of immune system function is required to personalize their treatment.

Currently, there is a significant gap in our understanding of immune response trajectories and the identification of markers for effective immune monitoring. Even the most promising markers, such as monocyte HLA-DR expression, require further clinical studies.

In addition, immune monitoring is likely to increase the cost of care for patients in the ICU, necessitating the development of alternative testing methods.

Management of patients based on their immune profile requires the development of personalized strategies for immune stimulation, treatment and prevention of infection.

Successful implementation of personalized interventions requires the identification of additional biomarkers for accurate assessment of immune status. Although some biomarkers are still in the experimental stage, they hold the promise for future clinical applications. Methods for monitoring immune status are expected to improve with Advances in modern biotechnology are expected to improve the methods for immune status monitoring.

## References


1. *Costabella F., Patel K.B., Adepoju A.V., Singh P., Mahmoud H.A.H., Zafar A., Patel T.,* et al. Healthcare cost and outcomes associated with surgical site infection and patient outcomes in low- and middle-income countries. *Cureus*. 2023; 15 (7): e42493. DOI: 10.7759/cureus.42493.
2. *Charalampous P., Haagsma J.A., Jakobsen L.S.. Gorasso V., Noguer I., Padron-Monedero A., Sarmiento R., et al.* Burden of infectious disease studies in Europe and the United Kingdom: a review of methodological design choices. *Epidemiol Infect*. 2023; 151: e19. DOI: 10.1017/S095026 8823000031. PMID: 36621004.
3. *Afzal M.S., Chennuri R.N., Naveed H., Bai B.R., Hanif R., Shahzad Z., Umer M., et al.* Comparison of clinical outcomes between culture-positive and culture-negative sepsis and septic shock patients: a meta-analysis. *Cureus*. 2023; 15 (2): e35416. DOI: 10.7759/cureus.35416. PMID: 36987463.
4. *Wang W., Liu C.F.* Sepsis heterogeneity. *World J Pediatr*. 2023; 19 (10): 919–927. DOI: 10.1007/s12519-023-00689-8. PMID: 36735197.
5. *Batool M., Galloway-Peña J.* Clinical metagenomics-challenges and future prospects. *Front Microbiol*. 2023; 14: 1186424. DOI: 10.3389/fmicb.2023.1186424. PMID: 37448579.
6. *Remick B.C., Gaidt M.M., Vance R.E.* Effector-triggered immunity. *Annu Rev Immunol*. 2023; 41: 453–481. DOI: 10.1146/annurev-immunol-101721-031732. PMID: 36750319.
7. *Martins Y.C., Ribeiro-Gomes F.L., Daniel-Ribeiro C.T.* A short history of innate immunity. *Mem Inst Oswaldo Cruz*. 2023; 118: e230023. DOI: 10.1590/0074-02760230023. PMID: 37162063.
8. *Belizaire R., Wong W.J., Robinette M.L., Ebert B.L.* Clonal haematopoiesis and dysregulation of the immune system. *Nat Rev Immunol*. 2023; 23 (9): 595–610. DOI: 10.1038/s41577-023-00843-3. PMID: 36941354.
9. *Cron R.Q., Goyal G., Chatham W.W.* Cytokine storm syndrome. *Annu Rev Med*. 2023; 74: 321–337. DOI: 10.1146/annurev-med-042921-112837. PMID: 36228171.
10. *Silva E.E., Skon-Hegg C., Badovinac V.P., Griffith T.S.* The calm after the storm: implications of sepsis immunoparalysis on host immunity. *J Immunol*. 2023; 211 (5): 711–719. DOI: 10.4049/jimmunol.2300171. PMID: 37603859.
11. *Nasrollahi H., Talepoor A.G., Saleh Z., Vakili M.A., Heydarinezhad O., Karami N., Noroozi M., et al.* Immune responses in mildly versus critically ill COVID-19 patients. *Front Immunol*. 2023; 14: 1077236. DOI: 10.3389/fimmu.2023. 1077236. PMID: 36793739.
12. *Li J., Zhang K., Zhang Y., Gu Z., Huang C.* Neutrophils in COVID-19: recent insights and advances. *Virol J*. 2023; 20 (1): 169. DOI: 10.1186/s12985-023-02116-w. PMID: 37533131.
13. *Fu X., Liu Z., Wang Y.* Advances in the study of immunosuppressive mechanisms in sepsis. *J Inflamm Res*. 2023; 16: 3967–3981. DOI: 10.2147/JIR.S426007. PMID: 37706064.
14. *Zhang W., Fang X., Gao C., Song C., He Y., Zhou T., Yang X., et al.* MDSCs in sepsis-induced immunosuppression and its potential therapeutic targets. *Cytokine Growth Factor Rev*. 2023; 69: 90–103. DOI: 10.1016/j.cytogfr.2022.07.007. PMID: 35927154.
15. *Kobayashi S.D., DeLeo F.R., Quinn M.T.* Microbes and the fate of neutrophils. *Immunol Rev*. 2023; 314 (1): 210–228. DOI: 10.1111/imr.13163. PMID: 36345955.
16. *Liu S., Duan C., Xie J., Zhang J., Luo X., Wang Q., Liang X., et al.* Peripheral immune cell death in sepsis based on bulk RNA and single-cell RNA sequencing. *Heliyon*. 2023; 9 (7): e17764. DOI: 10.1016/j.heliyon.2023.e17764. PMID: 37455967.
17. *Wu H., Tang T., Deng H., Chen D., Zhang C., Luo J., Chen S., et al.* Immune checkpoint molecule Tim-3 promotes NKT cell apoptosis and predicts poorer prognosis in sepsis. *Clin Immunol*. 2023; 254: 109249. DOI: 10.1016/j.clim.2023. 109249. PMID: 36736642.
18. *Huang L., Zhang X., Fan J., Liu X., Luo S., Cao D., Liu Y., et al.* EGFR promotes the apoptosis of $CD4^+$ T lymphocytes through TBK1/Glut1 induced Warburg effect in sepsis. *J Adv Res*. 2023; 44: 39–51. DOI: 10.1016/j.jare.2022.04.010. PMID: 35618635.
19. *Chao Y., Huang W., Xu Z., Li P., Gu S.* Effect of RUNX1/FOXP3 axis on apoptosis of T and B lymphocytes and immunosuppression in sepsis. *Open Med* (Wars). 2023; 18 (1): 20230728. DOI: 10.1515/med-2023-0728. PMID: 37636994.
20. *Yu D., Xie Y., Li X.* Based on the Hippo signaling pathway to explore the mechanism of autophagy in lung injury of acute respiratory distress syndrome induced by sepsis. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2023; 35 (8): 884–888. DOI: 10.3760/cma.j.cn121430-20220705-00633. PMID: 37593872.
21. *Yang L., Zhou L., Li F., Chen X., Li T., Zou Z., Zhi Y., et al.* Diagnostic and prognostic value of autophagy-related key genes in sepsis and potential correlation with immune cell signatures. *Front Cell Dev Biol*. 2023; 11: 1218379. DOI: 10.3389/fcell.2023.1218379. PMID: 37701780.
22. *Di C., Du Y., Zhang R. Zhang L., Wang S.* Identification of autophagy-related genes and immune cell infiltration characteristics in sepsis via bioinformatic analysis. *J Thorac Dis*. 2023; 15 (4): 1770–1784. DOI: 10.21037/jtd-23-312. PMID: 37197531.
23. *Yang Y.S., Zheng W.J., Liu C.Y., Chen W.-C., Xie W.-Z., He H.-F.* Mitophagy-related genes could facilitate the development of septic shock during immune infiltration. *Medicine (Baltimore)*. 2023; 102 (42): e35154. DOI: 10.1097/MD.00000 00000035154. PMID: 37861563.
24. *Mangalesh S., Dudani S., Malik A.* The systemic immune-inflammation index in predicting sepsis mortality. *Postgrad Med*. 2023; 135 (4): 345–351. DOI: 10.1080/00325481. 2022.2140535.PMID: 36287784.
25. *Kourilovitch M., Galarza-Maldonado C.* Could a simple biomarker as neutrophil-to-lymphocyte ratio reflect complex processes orchestrated by neutrophils? *J Transl Autoimmun*. 2022; 6: 100159. DOI: 10.1016/j.jtauto.2022.100159. PMID: 37396460.
26. *Zhao J., Dai R.S., Chen Y.Z., Zhuang Y.G.* Prognostic significance of lymphocyte subpopulations for ICU-acquired infections in patients with sepsis: a retrospective study. *J Hosp Infect*. 2023; 140: 40-45. DOI: 10.1016/j.jhin.2023.05.022. PMID: 37399906.
27. *Plebani M.* Why C-reactive protein is one of the most requested tests in clinical laboratories? *Clin Chem Lab Med*. 2023; 61 (9): 1540–1545. DOI: 10.1515/cclm-2023-0086. PMID: 36745137.

28. *Jiang X., Zhang C., Pan Y., Cheng X., Zhang W.* Effects of C-reactive protein trajectories of critically ill patients with sepsis on in-hospital mortality rate. *Sci Rep*. 2023; 13 (1): 15223. DOI: 10.1038/s41598-023-42352-2. PMID: 37709919.
29. *Ji S.-R., Zhang S.-H., Chang Y., Li H.-Y., Wang M.-Y., Zhu L., et al.* C-reactive protein: the most familiar stranger. *Immunol*. 2023; 210 (6): 699–707. DOI: 10.4049/jimmunol.2200831. PMID: 36881905.
30. *Plebani M.* Why C-reactive protein is one of the most requested tests in clinical laboratories? *Clin Chem Lab Med*. 2023; 61 (9): 1540–1545. DOI: 10.1515/cclm-2023-0086. PMID: 36745137.
31. *Saura O., Luyt C.-E.* Procalcitonin as a biomarker to guide treatments for patients with lower respiratory tract infections. *Expert Rev Respir Med*. 2023; 17 (8): 651–661. DOI: 10.1080/17476348.2023.2251394. PMID: 37639716.
32. *August B.A., Kale-Pradhan P.B., Giuliano C., Johnson L.B.* Biomarkers in the intensive care setting: a focus on using procalcitonin and C-reactive protein to optimize antimicrobial duration of therapy. *Pharmacotherapy*. 2023; 43 (9): 935–949. DOI: 10.1002/phar.2834. PMID: 37300522.
33. *Molano-Franco D., Arevalo-Rodriguez I., Muriel A., Del Campo-Albendea L., Fernández-García S., Alvarez-Méndez A., Simancas-Racines D., et al.,* SEPSIS-BIOMARKERS Collaborators. Basal procalcitonin, C-reactive protein, interleukin-6, and presepsin for prediction of mortality in critically ill septic patients: a systematic review and meta-analysis.. *Diagn Progn Res*. 2023; 7 (1): 15. DOI: 10.1186/ s41512-023-00152-2. PMID: 37537680.
34. *Long A., Kleiner A., Looney R.J.* Immune dysregulation. *J Allergy Clin Immunol*. 2023; 151 (1): 70–80. DOI: 10.1016/j.jaci.2022.11.001. PMID: 36608984.
35. *Das U.N.* Infection, inflammation, and immunity in sepsis. *Biomolecules*. 2023; 13 (9): 1332. DOI: 10.3390/biom13091332. PMID: 37759732.
36. *Afshar Z.M., Barary M., Babazadeh A., Pirzaman A.T., Hosseinzadeh R., Alijanpour A., AllahgholipourA., et al.* The role of cytokines and their antagonists in the treatment of COVID-19 patients. *Rev Med Virol*. 2023; 33 (1): e2372. DOI: 10.1002/rmv.2372. PMID: 35621229.
37. *Chen Y., Dong P., Zhang X.* [Research advance on the role of pro-inflammatory cytokines in sepsis]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. 2023; 35 (2): 212–216. DOI: 10.3760/cma.j.cn121430-20220919-00846. PMID: 36916385.
38. *Qin R., He L., Yang Z., Jia N., Chen R., Xie J., Fu W., et al.* Identification of parameters representative of immune dysfunction in patients with severe and fatal COVID-19 infection: a systematic review and meta-analysis. *Clin Rev Allergy Immunol*. 2023; 64 (1): 33–65. DOI: 10.1007/s12016-021-08908-8. PMID: 35040086.
39. *Яковенко М. П., Антипин Э. Э., Бочкарева Н. А., Королева Н.И., Дроботова Е.Ф., Недашковский Э.В.* Модифицированные блокады надключичного и грудных нервов при имплантации внутривенной портсистемы у онкологических пациентов. *Общая реаниматология*. 2023; 19 (3): 28–38. *Yakovenko M. P., Antipin E.E., Bochkareva N.A., Koroleva N.I., Drobotova E.F., Nedashkovsky E.V.* Modified supraclavicular and thoracic nerves blocks for implantation of intravenous port system in cancer patients. *General Reanimatology= Obshchaya Reanimatologya*. 2023; 19 (3): 28–38. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2023-3-28-38.
40. *Ратников В. А., Щеглов А. Н., Абрамовский С. В., Симутис И.С., Данилов М.С., Иванова Г.Г., Сыроватский А.А.* Предикторы клинической эффективности гемосорбции цитокинов при COVID-19. *Общая реаниматология*. 2023; 19 (1): 20–26. *Ratnikov V. A., Shcheglov A. N., Abramovsky S. V., Simutis I.S., Danilov M.S., Ivanova G.G., Syrovatsky A.A.* Predictors of clinical efficacy of cytokine hemoadsorption in COVID-19 (Clinical trial). *General Reanimatology=Obshchaya Reanimatologya*. 2023; 19 (1): 20–26. (in Russ.&Eng.). DOI: 10.15360/1813-9779-2023-1-2224.
41. *Румянцев А.Г., Демина О.М., Греченко В.В., Ганковская Л.В., Потекаев Н.Н.* Патогенетическое значение семейства ИЛ-10 при акне тяжелой степени. *Иммунология*. 2023; 44 (4): 463–470. *Rumyantsev A.G., Demina O.M., Grechenko V.V., Gankovskaya L.V., Potekaev N.N.* Pathogenetic significance of the IL-10 family in severe acne. *Immunology= Immunologiya*. 2023; 44 (4): 463–470. (in Russ.). DOI: 10.33029/0206-4952-2023-44-4-463-470.
42. *Порошина А.С., Шершакова Н.Н., Шиловский И.П., Кадушкин А.Г., Таганович А.Д., Гудима Г.О., Хаитов М.Р.* Роль ИЛ-25, ИЛ-33 и TSLP в развитии кортикостероидной резистентности. *Иммунология*. 2023; 44 (4): 500–510. *Poroshina A.S., Shershakova N.N., Shilovsky I.P., Kadushkin A.G., Tahanovich A.D., Gudima G.O., Khaitov M.R.* Role of IL-25, IL-33 and TSLP in the development of corticosteroid resistance. *Immunology = Immunologiya*. 2023; 44 (4): 500–510. (in Russ.). DOI: 10.33029/0206-4952-2023-44-4-500-510.
43. *Бязрова М.Г., Порошина А.С., Сухова М.М., Фролов Е.А., Шилкина А.Б., Латышева Е.А., Латышева Т.В., с соавт.* Продукция цитокинов наивными В-лимфоцитами и В-клетками памяти при стимуляции *in vitro*. *Иммунология*. 2023; 44 (5): 575-585. *Byazrova M.G., Poroshina A.S., Sukhova M.M., Frolov E.A., Shilkina A.B., Latysheva E.A., Latysheva T.V., et al.* Production of cytokines by *in vitro* stimulated naive B lymphocytes and memory B cells. *Immunology= Immunologiya*. 2023; 44 (5): 575–585. (in Russ.). DOI: 10.33029/0206-4952-2023-44-5-575-585.
44. *Pham H.M., Nguyen D.L.M., Duong M.C., Tran L.T., Pham T.T.N.* Diagnostic value of neutrophil CD64 in sepsis patients in the intensive care unit: a cross-sectional study. *Diagnostics (Basel)*. 2023; 13 (8): 1427. DOI: 10.3390/diagnostics13081427. PMID: 37189528.
45. *Han J., Zhang Y., Ge P., Dakal T.C., Wen H., Tang S., Luo Y., et al.* Exosome-derived CIRP: an amplifier of inflammatory diseases. *Front Immunol*. 2023; 14: 1066721. DOI: 10.3389/fimmu.2023.1066721. PMID: 36865547.
46. *Scott J., Trevi L., McNeil H., Ewen T., Mawson P., McDonald D., Filby A., et al.* Role of immunosuppression in an antibiotic stewardship intervention and its association with clinical outcomes and anti-

biotic use: protocol for an observational study (RISC-sepsis). *BMJ Open*. 2022; 12 (12): e068321. DOI: 10.1136/bmjopen-2022-068321. PMID: 36600326.
47. *Zou S., Jie H., Han X., Wang J.* The role of neutrophil extracellular traps in sepsis and sepsis-related acute lung injury. *Int Immunopharmacol*. 2023; 124 (Pt A): 110436. DOI: 10.1016/j.intimp.2023.110436. PMID: 37688916.
48. *Ansari M.A., Das S., Rai G., Singh P.K., Lahan S., Tyagi A., Alamer E., et al.* Low monocytic HLA-DR expression in critically ill patients of sepsis: an indicator for antimicrobial and/or immunomodulatory intervention. *Transpl Immunol*. 2023; 81: 101942. DOI: 10.1016/j.trim.2023.101942. PMID: 37866671.
49. *Joshi I., Carney W.P., Rock E.P.* Utility of monocyte HLA-DR and rationale for therapeutic GM-CSF in sepsis immunoparalysis. *Front Immunol*. 2023; 14: 1130214. DOI: 10.3389/fimmu.2023.1130214. PMID: 36825018.
50. *Quirant-Sánchez B., Plans-Galván O., Lucas E., Argudo E., Martinez-Cáceres E.M., Arméstar F.* HLA-DR expression on monocytes and sepsis index are useful in predicting sepsis. *Biomedicines*. 2023; 11 (7): 1836. DOI: 10.3390/biomedicines11071836. PMID: 37509475.
51. *Ostrand-Rosenberg S., Lamb T.J., Pawelec G.* Here, there, and everywhere: myeloid-derived suppressor cells in immunology. *J Immunol*. 2023; 210 (9): 1183–1197. DOI: 10.4049/jimmunol.2200914. PMID: 37068300.
52. *Wang F., Cui Y., He D., Gong L., Liang H.* Natural killer cells in sepsis: friends or foes? *Front Immunol*. 2023; 14: 1101918. DOI: 10.3389/fimmu.2023.1101918. PMID: 36776839.
53. *Etemad B., Sun X., Li Y., Melberg M., Moisi D., Gottlieb R., Ahmed H., et al.* HIV post-treatment controllers have distinct immunological and virological features. *Proc Natl Acad Sci USA*. 2023; 120 (11): e2218960120. DOI: 10.1073/pnas. 2218960120. PMID: 36877848.
54. *Wu H., Tang T., Deng H., Chen D., Zhang C., Luo J., Chen S., et al.* Immune checkpoint molecule Tim-3 promotes NKT cell apoptosis and predicts poorer prognosis in sepsis. *Clin Immunol*. 2023; 254: 109249. DOI: 10.1016/j.clim.2023. 109249. PMID: 36736642.
55. *Sohn H., Cooper M.A.* Metabolic regulation of NK cell function: implications for immunotherapy. *Immunometabolism (Cobham)*. 2023; 5 (1): e00020. DOI: 10.1097/IN9.00000000 00000020. PMID: 36710923.
56. *Yao Y.M., Zhang H., Wu Y.* [Novel strategy of sepsis immunomodulation targeting dendritic cells]. *Zhonghua Shao Shang Yu Chuang Mian Xiu Fu Za Zhi*. 2023; 39 (7): 606–611. DOI: 10.3760/cma.j.cn501225-20230321-00087. PMID: 37805688.
57. *Zhao F.-Z., Gu W.-J., Li L.-Z., Qu Z.-K., Xu M.-Y., Liu K.,Zhang F., et al.* Cannabinoid receptor 2 alleviates sepsis-associated acute lung injury by modulating maturation of dendritic cells. *Int Immunopharmacol*. 2023; 123: 110771. DOI: 10.1016/j.intimp.2023.110771. PMID: 37582314.
58. *Wu Y., Chen L., Qiu Z., Zhang X., Zhao G., Lu Z.* PINK1 protects against dendritic cell dysfunction during sepsis through the regulation of mitochondrial quality control. *Mol Med*. 2023; 29 (1): 25. DOI: 10.1186/s10020-023-00618-5. PMID: 36809929.
59. *Bénard A., Hansen F.J., Uhle F., Klösch B., Czubayko F., Mittelstädt A., Jacobsen A., et al.* Interleukin-3 protects against viral pneumonia in sepsis by enhancing plasmacytoid dendritic cell recruitment into the lungs and T cell priming. *Front Immunol*. 2023; 14: 1140630. DOI: 10.3389/fimmu.2023.1140630. PMID: 36911737.
60. *Zhang T., Lian G., Fang W., Tian L., Ma W., Zhang J., Meng Z., et al.* Comprehensive single-cell analysis reveals novel anergic antigen-presenting cell subtypes in human sepsis. *Front Immunol*. 2023; 14: 1257572 DOI: 10.3389/fimmu.2023.1257572. PMID: 37781404.
61. *Li J.-B., Xie M.-R., Duan M.-L., Yu Y.-N., Hang C.-C., Tang Z.-R., Li C.-S.* Over-expression of programmed death-ligand 1 and programmed death-1 on antigen-presenting cells as a predictor of organ dysfunction and mortality during early sepsis: a prospective cohort study. *World J Emerg Med*. 2023; 14 (3): 179–185. DOI: 10.5847/wjem.j.1920-8642.2023.041. PMID: 37152526.
62. *Turner S., Raisley B., Roach K., Bajaña S., Munroe M.E., James J.A., Coggeshall K.M., et al.* Gram-positive bacteria cell wall peptidoglycan polymers activate human dendritic cells to produce IL-23 and IL-1β and promote $T_H17$ cell differentiation. *Microorganisms*. 2023; 11 (1): 173. DOI: 10.3390/microorganisms11010173. PMID: 36677464.
63. *Liu H., Li J.-F., Zhang L.-M., Wang H.-H., Wang X.-Q., Kiu G.-Q., Du H.-B., et al.* Posthemorrhagic shock mesenteric lymph impairs splenic dendritic cell function in mice. *Shock*. 2023; 59 (2): 256–266. DOI: 10.1097/SHK.00000000 00002056. PMID: 36427100.
64. *Finfer S., Venkatesh B., Hotchkiss R.S., Sasson S.C.* Lymphopenia in sepsis- an acquired immunodeficiency? *Immunol Cell Biol*. 2023; 101 (6): 535–544. DOI: 10.1111/imcb.12611. PMID: 36468797.
65. *Winer H., Rodrigues G.O.L, Hixon J.A., Aielo F.B., Hsu T.C., Wachter B.T., Li W., et al.* IL-7: comprehensive review. *Cytokine*. 2022; 160: 156049. DOI: 10.1016/j.cyto.2022.156049. PMID: 36201890.
66. *Gao Y., Ya Y., Zhang X., Chen F., Meng X.-L., Chen X.-S., Wang C.-L., et al.* Regulatory T cells: angels or demons in the pathophysiology of sepsis? *Front. Immunol*. 2022; 13: 829210. DOI: 10.3389/fimmu.2022. 829210. PMID: 35281010.
67. *Li X.-Y., Liu M., Fu Y-J., Jiang Y.-J., Zhang Z.-N.* Alterations in levels of cytokine following treatment to predict outcome of sepsis: a meta-analysis. *Cytokine*. 2023; 161: 156056. DOI: 10.1016/j.cyto.2022.156056. PMID: 36240721.
68. *Wautier J.L., Wautier M.P.* Pro- and anti-Inflammatory prostaglandins and cytokines in humans: a mini review. *Int J Mol Sci*. 2023; 24 (11): 9647. DOI: 10.3390/ijms24119647. PMID: 37298597.
69. *Barber G., Tanic J., Leligdowicz A.* Circulating protein and lipid markers of early sepsis diagnosis and prognosis: a scoping review. *Curr Opin Lipidol*. 2023; 34 (2): 70–81. DOI: 10.1097/MOL.0000000000000870. PMID: 36861948.
70. *Korzhenevich J., Janowska I., van der Burg M., Rizzi M.* Human and mouse early B cell development: So similar but so different. *Immunol Lett*. 2023; 261: 1–12. DOI: 10.1016/j.imlet.2023.07.004. PMID: 37442242.

71. *Dong X., Tu H., Qin S., Bai X., Yang F., Li Z.* Insights into the roles of B cells in patients with sepsis. *J Immunol Res.* 2023; 2023: 7408967. DOI: 10.1155/2023/7408967. PMID: 37128298.
72. *Pan B., Sun P., Pei R., Lin F., Cao H.* Efficacy of IVIG therapy for patients with sepsis: a systematic review and meta-analysis. *J Transl Med.* 2023; 21 (1): 765. DOI: 10.1186/s12967-023-04592-8. PMID: 37898763.
73. *Du K., Hao S., Luan H.* Retracted: expression of peripheral blood DCs CD86, CD80, and Th1/Th2 in sepsis patients and their value on survival prediction. *Comput Math Methods Med.* 2023; 2023: 9832093. DOI: 10.1155/2023/ 9832093. PMID: 37416269.
74. *Dong X., Tu H., Bai X., Qin S., Li Z.* Intrinsic/extrinsic apoptosis and pyroptosis contribute to the selective depletion of B cell subsets in septic shock patients. *Shock.* 2023; 60 (3): 345–353. DOI: 10.1097/SHK.0000000000002174. PMID: 37477437.
75. *Sharma P., Goswami S., Raychaudhuri D., Siddiqui B.A., Singh P., Nagarajan A., Liu J.* Immune checkpoint therapy-current perspectives and future directions. *Cell.* 2023; 186 (8): 1652–1669. DOI: 10.1016/j.cell.2023.03.006. PMID: 37059068.
76. *Liu D., Huang S.Y., Sun J.H., Zhang H.-C., Cai Q.-L., Gao C., Li L.* Sepsis-induced immunosuppression: mechanisms, diagnosis and current treatment options. *Mil Med Res.* 2022; 9 (1): 56. DOI: 10.1186/s40779-022-00422-y. PMID: 36209190.
77. *van den Haak D.A.C., Otten L.S., Koenen HJ.PM., Smeets R.L., Piet B., Pickkers P., Kox M., et al.* Evidence-based rationale for low dose nivolumab in critically ill patients with sepsis-induced immunosuppression. *Clin Transl Sci.* 2023; 16 (6): 978–986. DOI: 10.1111/cts.13503. PMID: 37002646.
78. *Kim G.-R., Choi J.-M.* Current understanding of cytotoxic T lymphocyte antigen-4 (CTLA-4) signaling in T-cell biology and disease therapy. *Mol Cells.* 2022; 45 (8): 513–521. DOI: 10.14348/molcells.2022.2056. PMID: 35950451.
79. *Bailly C., Thuru X., Goossens L., Goossens J.-F.* Soluble TIM-3 as a biomarker of progression and therapeutic response in cancers and other of human diseases. *Biochem Pharmacol.* 2023; 209: 115445. DOI: 10.1016/j.bcp.2023.115445. PMID: 36739094.
80. *Ibrahim R., Saleh K., Chahine C., Khoury R., Khalife N., Cesne A.L.* LAG-3 Inhibitors: novel immune checkpoint inhibitors changing the landscape of immunotherapy. *Biomedicines.* 2023; 11 (7): 1878. DOI: 10.3390/ biomedicines11071878. PMID: 37509517.
81. *Sordo-Bahamonde C., Lorenzo-Herrero S., Granda-Díaz R., Martínez-Pérez A., Aguilar-García C., Rodrigo J.P., García-Pedrero J.M., et al.* Beyond the anti-PD-1/PD-L1 era: promising role of the BTLA/HVEM axis as a future target for cancer immunotherapy. *Mol Cancer.* 2023; 22 (1): 142. DOI: 10.1186/s12943-023-01845-4. PMID: 37649037.
82. *García Melián M.F., Moreno M., Cerecetto H., Calzada V.* Aptamer-based immunotheranostic strategies. *Cancer Biother Radiopharm.* 2023; 38 (4): 246–255. DOI: 10.1089/cbr.2022.0064. PMID: 36603108.
83. *Rienzo M., Skirecki T., Monneret G., Timsit J.-F.* Immune checkpoint inhibitors for the treatment of sepsis: insights from preclinical and clinical development. *Expert Opin Investig Drugs.* 2022; 31 (9): 885–894. DOI: 10.1080/13543784.2022.2102477. PMID: 35944174.


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