Subphenotypic Classification of Immune Response in Sepsis: Predicting Mortality and Guiding Future Personalized Immunotherapy

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ABSTRACT

The most recent definition of sepsis highlights the dysregulation of the host's immune response to infection, which varies between individual hosts, with patients predominantly presenting with either hyperinflammation, immunoparalysis, or a combination of both states. Therefore, management strategies must be tailored to accommodate the heterogeneity of patients with sepsis, as these conditions are associated with distinct prognoses and therapeutic approaches. Identification of the immune response in patients with sepsis can be achieved through advanced techniques, such as gene expression profiling or, more simply, through a subphenotypic approach. This article introduces a subphenotypic classification of the sepsis immune response into macrophage activation-like syndrome (MALS), where pathological macrophage activation leads to excessive hyperinflammation, immunoparalysis, or neither. Patients are classified using serum ferritin levels and monocyte HLA-DR expression, which is assessed using peripheral blood. This classification demonstrates significant differences in survival across groups, which is attributed to their distinct underlying biological processes. Immunotherapeutic options also differ for these three groups. In the future, such immune response classifications will be valuable in sepsis management algorithms for personalized prognostication and therapy.

Keywords: *sepsis, macrophage activation-like syndrome, immunoparalysis, subphenotype.*

INTRODUCTION

Sepsis is a leading cause of mortality in infection. An observational study conducted at four major centers in Indonesia revealed that the in-hospital mortality rate related to sepsis was 58.3% while the global mortality rate was 27%, which suggests that the number of deaths due to sepsis in Indonesia is higher when compared to developed nations.[1,2]

The most recent definition of sepsis (Sepsis-3) emphasizes the dysregulation of the host response to infection. Instead of eradicating the infection, the host response causes tissue and organ damage, leading to life-threatening organ dysfunction. The dysregulated response varies between individual hosts; therefore, management strategies must be tailored to accommodate the heterogeneity of patients with sepsis.[3,4]

From an immunological and inflammatory perspective, sepsis is characterized by immune dysregulation, which can manifest as hyperinflammation (i.e., the classical sepsis subphenotype) or hypoinflammation, also known as immunoparalysis. In younger patients without

any comorbidities, hyperinflammation may dominate the host response, which contributes to organ dysfunction and early death. In older adults with multimorbidity, the inflammatory response to infection may be insufficient to directly cause organ dysfunction. In this immunoparalytic group, death from sepsis is typically delayed.[5] However, given the heterogeneity of the condition and the numerous factors involved, it is difficult to distinguish patients with hyperinflammation from those with immunoparalysis. This difficulty has led to the notion that specific biomarkers are needed to select and differentiate between immune responses in patients with sepsis.

Studies of sepsis in developed countries have utilized an endotypic approach, based on underlying biological mechanisms, to cluster the immune responses of patients with sepsis through gene expression analysis.[6,7] In developing countries, however, simpler biomarkers are required for such classification. Biomarkers based on a subphenotypic approach, which are grounded in observable characteristics, offer a feasible alternative.

BIOMARKERS OF THE IMMUNE RESPONSE IN SEPSIS

Various biomarkers are utilized in sepsis for diagnosis, identifying the source of infection, guiding therapy, and determining prognosis. Recent studies increasingly use biomarkers to classify patients with sepsis based on their immune response. This classification helps determine the patients' immune state, providing a prognosis for care and guiding future therapeutic options.

Ferritin as a Biomarker of Hyperinflammation and Macrophage Activation-Like Syndrome

Hyperinflammation in patients with sepsis is typically identified by measuring proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-8, and plasminogen activator inhibitor 1. IL-6 also triggers the liver to produce acute-phase reactants, such as C-reactive protein.[8]

Novel biomarkers recently used include procalcitonin, pentraxin-3, complement C5a, CD64 expression on neutrophil surfaces, CD11b, triggering receptor expressed on myeloid cells-1, receptor for advanced glycation end-products, high-mobility group box 1, which is a protein released by necrotic cells, and ferritin,[9] which is released in physiological, pathophysiological, and pathobiological conditions. Hence, ferritin is a key biological marker of macrophage-mediated inflammation.

During infection, ferritin is produced by macrophages following nuclear factor-κB (NF-κB) activation, which is induced by IL-1 and TNFα. Ferritin functions to sequester iron from iron-loving bacteria and prevent oxidative damage caused by iron to the host's macrophage DNA. Furthermore, ferritin can initiate a positive feedback loop in inflammation. In this loop, stimulation of Toll-like receptor 9 (TLR9) by damage-associated molecular patterns (DAMPs), viral DNA, or other infections leads to the production of IL-1 and IL-18 mediated by the inflammasome. These cytokines further stimulate ferritin production, which in turn enhances the regulation of all TLRs, driving additional inflammatory cascades. Elevated ferritin levels can ultimately result in liver damage by macrophages, anergy, and failure of lymphopoiesis.[10,11]

Rosario et al. described a pathobiological condition known as hyperferritinemia syndrome, which is characterized by increased ferritin production, not just as a secondary response to initial proinflammatory conditions, but also by the involvement of ferritin itself in the pathogenesis of worsening disease as described above. Hyperferritinemia syndrome includes macrophage activation syndrome (MAS), adult-onset Still's disease, catastrophic antiphospholipid syndrome, and septic shock. In hyperferritinemia syndrome, a large amount of iron-poor ferritin acts as an immunomodulator, inducing proinflammatory cytokines (activating NF-κB and enhancing the expression of proinflammatory mediators) while simultaneously causing immunoparalysis (suppressing delayed-type hypersensitivity reactions, inhibiting antibody production by B lymphocytes, reducing phagocytosis by granulocytes, and regulating granulomonocytopoiesis).[12]

The main manifestations of MAS include fever, hepatosplenomegaly, hepatobiliary dysfunction, coagulopathy, bicytopenia or pancytopenia, increased triglycerides, and hemophagocytosis in the bone marrow. MAS can occur as a complication of hematologic malignancies, autoimmune diseases, and infections (particularly viral infections). Its pathogenesis is not fully understood but is known to be associated with excessive macrophage and natural killer (NK) cell activation, which leads to the excessive secretion of IL-1β, IL-6, IL-18, ferritin (>6,000 ng/mL), interferon-γ (IFN-γ), and elevated soluble CD163 (sCD163) levels.[13,14]

In patients with sepsis, MAS is specifically termed macrophage activation-like syndrome (MALS), which was first studied in a cohort by the Hellenic Sepsis Study Group. The criteria for MALS in this study did not include bone marrow biopsy, as this procedure is difficult to perform in critically ill patients. Patients with sepsis were classified as having MALS if their HScore was >151 or if they exhibited hepatobiliary dysfunction along with disseminated intravascular coagulation. The HScore is a scoring system used for diagnosing hemophagocytic lymphohistiocytosis (HLH).[15]

No study has specifically investigated the risk factors for developing MALS in sepsis. However, in the ProCESS study, a cohort involving 1,177 patients with septic shock, the MALS group had higher Charlson Comorbidity Index scores and a greater proportion of patients with chronic liver disease, renal failure, and malignancies compared to the control group.[16]

Ferritin is a key diagnostic and biological marker for MALS. Ferritin levels, ≥2,000 ng/mL, are one of the HScore parameters. In the cohort study by the Hellenic Sepsis Study Group, ferritin concentrations >4,420 ng/mL facilitated the diagnosis of MALS, with a specificity of 97.1% and a negative predictive value of 98%. Elevated ferritin levels were also associated with increased IL-6, IL-18, IFN-γ, and sCD163, as well as a reduced IL-10/TNFα ratio, which suggests that elevated ferritin may indicate a predominance of the proinflammatory phenomenon, supporting early diagnosis of MALS. Therefore, the pathobiology and management of sepsis with hyperferritinemia may differ from sepsis without hyperferritinemia (**Figure 1**).[17,18]

Various conditions other than sepsis can cause hyperferritinemia, which can result from iron overload or conditions unrelated to iron accumulation. Etiologies of hyperferritinemia due to iron overload include hereditary hemochromatosis, anemia with iron overload, and iatrogenic causes (such as red blood cell transfusion or iron supplementation). Etiologies of hyperferritinemia unrelated to iron overload include cell damage, metabolic syndrome, excessive alcohol consumption, malignancies, and various infections and inflammatory conditions. Among these etiologies, conditions that may lead to hyperferritinemia >5,000 ng/mL include infections by various pathogens (e.g., bacteria, fungi, viruses, and parasites), HLH, hepatitis of various causes, posttransfusion iron overload syndrome, malignancies, cytokine release syndrome, rheumatic or inflammatory diseases (e.g., drug rash with eosinophilia and systemic symptoms, Sweet's syndrome, Castleman's disease, polymyalgia rheumatica), and acute hemolysis (e.g., hemoglobinopathies, autoimmune hemolytic anemia, thrombotic microangiopathies).[19] These conditions should be considered when measuring ferritin to assess MALS in sepsis.

Monocyte HLA-DR Expression as a Biomarker of Immunoparalysis

The detection of sepsis-induced immunoparalysis is not straightforward. The clinical manifestation transitioning from early hyperinflammation to later immunoparalysis is not easily identifiable in practice. Thus, there is a need to identify biomarkers to support the diagnosis of immunoparalysis in sepsis.

Biomarkers that can assist in diagnosing immunoparalysis may be derived from simple laboratory tests or more complex examinations. Simpler tests include the increased number of immature neutrophils, reduced expression of monocyte HLA-DR (mHLA-DR), lymphopenia, elevated neutrophil-to-lymphocyte ratio, and viral reactivation. The first two tests assess innate immunity function, while the latter two evaluate

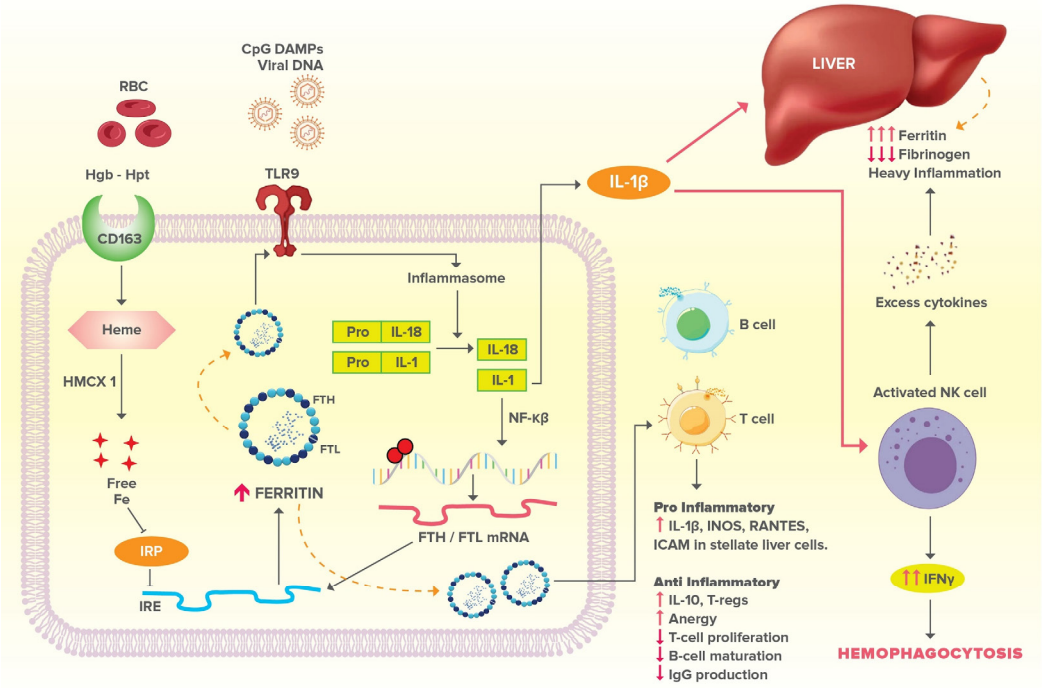

Figure 1. Concept of MALS in Sepsis. Ferritin stimulates TLR, leading to excessive production of IL-1β, which causes a cytokine storm and the release of CD163 from the macrophage cell membrane. Cytokines further stimulate ferritin production by the liver, leading to liver dysfunction, while IL-1β causes excessive production of IFNγ by NK cells, triggering hemophagocytosis. CpG, cytosine poly guanosine; Fe, iron; FTH, ferritin heavy chain; FTL, ferritin light chain; Hgb–Hpt, hemoglobin–haptoglobin complex; HMOX1, heme oxygenase 1; ICAM, intercellular adhesion molecule; iNOS, inducible nitric oxide synthase; IRE, iron responsive element; IRP, iron responsive protein; RANTES, regulated on activation, normal T cell expressed and secreted. Modified with permission from "Why and how is hyperferritinemic sepsis different from sepsis without hyperferritinemia?" by Carcillo JA, Kernan KK, Horvat CM, Simon DW, Aneja RK. *Pediatr Crit Care Med*. 2020;21(5):509–12

adaptive immune function.[20]

A reduction in monocyte sCD127, endotoxin tolerance in monocytes (in response to lipopolysaccharide antigen stimulation), increased monocyte programmed death ligand 1 (PD-L1) expression, elevated IL-10/TNF ratio, and a reduction in dendritic cell count suggest immunoparalysis in the innate immune system. Similarly, increased concentrations of IL-10, IL-13, IL-1 receptor antagonist (IL-1ra), and transforming growth factor-β (TGF-β) indicate suppression of the innate immune system. For adaptive immunity, an increase in cytotoxic T lymphocyte antigen-4 (CTLA-4), B and T lymphocyte attenuator (BTLA), lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin protein 3 (TIM-3), programmed death 1 (PD1) expression on $CD4^+$ and $CD8^+$ T cells, CD127, an increased level of regulatory T cells (Treg; $CD4^+CD25^+$ cells), and a reduction in T cell proliferation indicate immunoparalysis. Transcriptomic analysis of CD74 and CX3CR1 serves as a markers of both innate and adaptive immunoparalysis in sepsis.[21]

Moreover, in various studies, immunoparalysis is being assessed through genomic tests, such as the detection of single nucleotide polymorphisms associated with TLR and other immune responses in addition to transcriptomic analysis to classify patients with sepsis into specific endotypes based on their immune response expression and metabolomics, which evaluates macrophage and T cell metabolic failure.[22]

During pathogen infection, the innate immune response serves as the first line of defense. Neutrophils and monocytes recognize pathogen-associated molecular patterns (PAMPs) and DAMPs. This interaction induces mononuclear phagocytic cells to release various proinflammatory cytokines to recruit and activate other immune cells. Mononuclear phagocytes also express major histocompatibility complex (MHC) class

II molecules, which activate antigen-specific T helper lymphocytes and secrete cytokines to activate other cells. In contrast, neutrophils do not perform antigen presentation to lymphocytes.[23]

The *MHC* gene on chromosome 6 encodes several MHC class II proteins, including HLA-DP, HLA-DQ, and HLA-DR. These proteins were initially identified as transplantation antigens, which serve as targets for immune rejection of transplant tissues. During infection, antigen-presenting cells (APCs) phagocytose pathogens, digest them, and generate peptides that bind with intracellular MHC class II proteins, such as HLA-DR. The peptide–MHC complex is transported to the cell surface, where it mediates antigen recognition by $CD4^+$ T helper lymphocytes. These T helper cells subsequently enhance the adaptive immune response by activating $CD8^+$ cytotoxic T lymphocytes, targeting infected cells, and B lymphocytes that produce specific antibodies. Since HLA-DR serves as a bridge between innate mononuclear phagocytes and antigen-specific T lymphocytes, reduced HLA-DR expression leads to impaired antigen presentation and reduced activation of the adaptive immune response.[24]

Both the innate and adaptive immune systems undergo alterations in sepsis, resulting in variable cytokine levels. It is hypothesized that myeloid proliferation due to persistent cytokine levels leads to rapid cell division, which depletes the metabolic capacity of newly formed mononuclear phagocytes compared to normal cells. Therefore, these immature monocytes cannot perform normal innate immune functions due to their low metabolic capacity. Consequently, these monocytes appear immunosuppressive, contributing to the immunoparalysis seen in sepsis (**Figure 2**).[25]

Flow cytometry is used to identify and

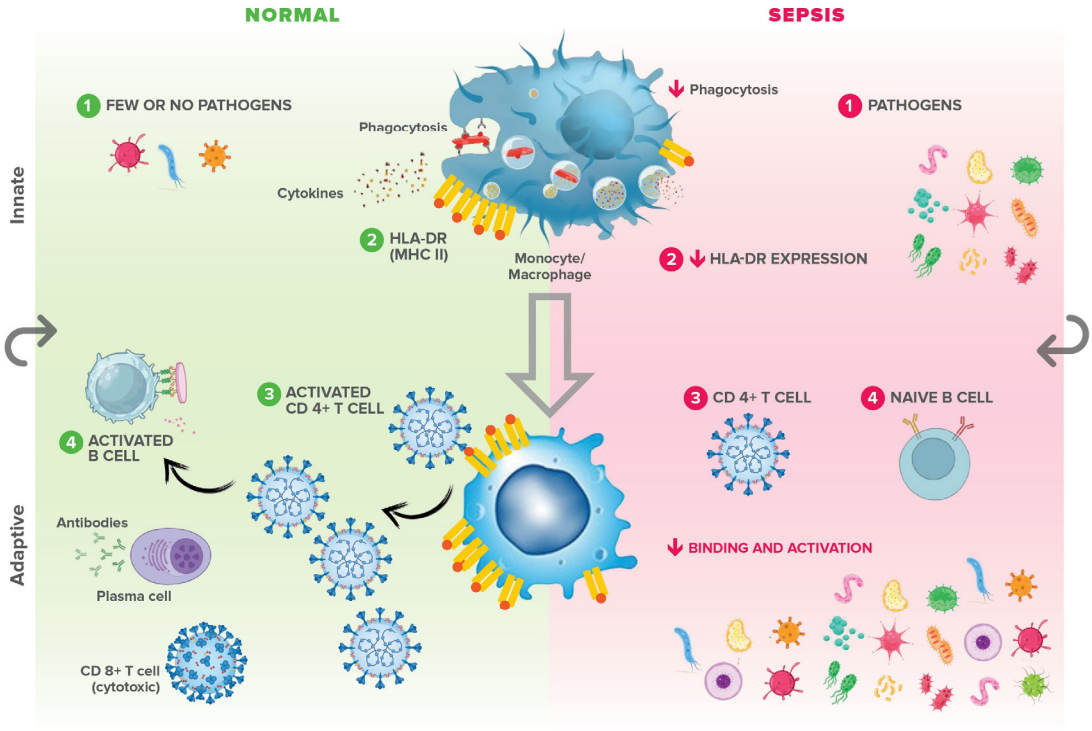

Figure 2. Monocyte and HLA-DR Function in Sepsis Compared to Healthy Individuals. (1) Monocytes/macrophages respond to pathogens through phagocytosis and cytokine secretion. In sepsis, dysfunctional monocytes/macrophages show reduced phagocytosis and a variable cytokine profile. (2) Phagocytosed pathogens are destroyed, combined as peptides with MHC class II molecules (e.g., HLA-DR isotype), and localized to the cell surface. In sepsis, dysfunctional monocytes/macrophages express lower levels of antigen-bound HLA-DR protein. (3) The peptide–MHC complex binds to $CD4^+$ helper T cells to activate the adaptive immune response, triggering cytokine release. In sepsis, antigen presentation is ineffective; hence, $CD4^+$ T cells remain unactivated. Therefore, the adaptive immune response is ineffective at eradicating pathogens. (4) Activated $CD4^+$ helper T cells undergo clonal expansion, activate $CD8^+$ T cells, and mediate B cell activation. In sepsis, naive B cells are not activated by $CD4^+$ T cells, and plasma cells that produce antibodies are not generated. Modified from "Utility of monocyte HLA-DR and rationale for therapeutic GM-CSF in sepsis immunoparalysis" by Joshi I, Carney WP, Rock EP. *Front Immunol.* 2023;14:1130214.

quantify HLA-DR expression. In addition to monocytes, several other cells also express HLA-DR, such as dendritic cells, macrophages, B cells, and T cells. Since sepsis requires the quantification of HLA-DR specifically on monocytes (i.e., mHLA-DR), an additional procedure is necessary, which involves staining for CD14 as a marker of monocytes. The combination of CD14 and HLA-DR staining is used to quantify $CD14^+$ monocytes. The results can be displayed as the percentage of $CD14^+$ monocytes expressing HLA-DR or as the mean fluorescence intensity of HLA-DR on $CD14^+$ monocytes. The latest quantitative measurement yields mHLA-DR expression in terms of antibody binding per cell (Ab/c), representing the amount of HLA-DR protein on $CD14^+$ monocytes.[26]

Using flow cytometry, it has been established that monocytes and macrophages express HLA-DR at a level of 15,000–60,000 antibody bindings per cell (Ab/c) under normal conditions.[27] Several studies use a cutoff point of mHLA-DR <10,000 Ab/c and <5,000–8,000 Ab/c to define moderate and severe immunoparalysis in sepsis, respectively.[28,29]

An alternative method for assessing mHLA-DR in diagnosing immunoparalysis in sepsis is the use of polymerase chain reaction (PCR) for HLA-DR, measuring myeloid-derived suppressor cells (MDSCs)—monocytes with low HLA-DR expression—and serial dynamic measurements of mHLA-DR.[25]

Reduced expression of mHLA-DR in patients with sepsis has been linked to a higher incidence of secondary infections and higher mortality. A study that performed serial mHLA-DR measurements concluded that patients with sepsis who showed improvement in mHLA-DR expression had a better prognosis than those whose mHLA-DR expression either did not increase, increased slowly, or decreased during hospitalization. Another study on intensive care unit (ICU) patients showed that low or persistently low mHLA-DR was associated with the occurrence of secondary infections during hospitalization. Measuring HLA-DR as a predictor of secondary infections was found to be superior to measuring leukocyte differential counts, such as lymphocyte and monocyte counts.[29,30]

Diagnosis of Immune Response in Sepsis

While several studies have grouped patients with sepsis based on their clinical presentation and biomarkers, few studies have categorized patients with sepsis specifically based on their immune responses. Classifying patients with sepsis based on their immune response subphenotype is important for determining appropriate therapy, estimating disease progression, and predicting survival.

The PROVIDE (a Personalized Randomized *trial* Of Validation and restoration of Immune Dysfunction in severE infections and *Sepsis) randomized clinical trial* classified adult patients with sepsis according to their immune response conditions. This study used plasma ferritin values and mHLA-DR expression to classify patients into three groups: MALS (ferritin >4,420 ng/mL), immunoparalysis (mHLA-DR <5,000 Ab/c and ferritin ≤4,420 ng/mL), and unclassified (mHLA-DR ≥5,000 Ab/c and ferritin ≤4,420 ng/mL). The mHLA-DR cutoff point of 5,000 Ab/c used in this study was determined based on confirmation with other markers of immunoparalysis, such as TNFα secretion from stimulated mononuclear cells. Patients with MALS had the highest mortality rate, 79.1%, followed by immunoparalysis at 66.9%.[28]

The classification of immune responses used in the PROVIDE study is being applied in an ongoing double-blind clinical trial, ImmunoSep (Personalised Immunotherapy in Sepsis; ClinicalTrials.gov NCT04990232). Patients who have sepsis with MALS will receive recombinant IL-1ra to suppress their proinflammatory response, while patients who have sepsis with immunoparalysis will be treated with recombinant human IFNγ to enhance their proinflammatory response.[31]

To date, no other studies have classified patients with sepsis into these three subphenotypes. Most sepsis studies typically focus on a single inflammatory subphenotype at a time or perform broad subphenotypic classification without considering the specific immune response.

Sepsis Outcomes Based on Immune Response

The immune response of patients with sepsis at the time of admission will influence disease progression and prognosis. Patients who present with hyperinflammation, particularly MALS, and immunosuppression/immunoparalysis will show different clinical manifestations, disease progression, and outcomes during hospitalization.

A systematic review and meta-analysis on patients with sepsis concluded that proinflammatory conditions, indicated by increased TNFα concentrations, were associated with higher 28-day mortality.[32] Another meta-analysis demonstrated that low-dose steroid administration to regulate the proinflammatory response decreased mortality, shortened hospital stay, accelerated shock resolution, and improved organ dysfunction scores in patients with sepsis.[33]

In contrast to these studies, an older study on sepsis found no correlation between cytokine levels and mortality.[34] Therefore, while hyperinflammation affects sepsis outcomes, many other factors contribute to the complexity of the outcomes, such as the presence of immunosuppression.

Immunosuppression or immunoparalysis is more often associated with long-term mortality and the occurrence of secondary or nosocomial infections during hospitalization. Persistent lymphopenia is a predictor of higher mortality, nosocomial infections, and a higher risk of chronic infections in sepsis.[35] Increased levels of Tregs, PD-1, and PD-L1 in peripheral blood are associated with long-term mortality in sepsis. Fluctuations in mHLA-DR expression can not only assess immune status but also predict outcomes in patients with sepsis.[36]

Immune Response Determines Future Personalized Immunotherapy in Sepsis

A one-size-fits-all approach to sepsis therapy is no longer appropriate. In the coming decades, sepsis treatment will shift toward personalized medicine, where therapy is tailored to the individual based on their dominant subphenotype and/or endotype.[37]

The immune response is one of the key factors in selecting immunotherapy during sepsis treatment. On the one hand, it is evident that some patients with sepsis do not die due to hyperinflammatory responses; therefore, suppressing the immune response may not be an effective strategy for all patients. On the other hand, it is known that a small subset of patients with hyperinflammation will survive if they receive immunosuppressive therapy. Therefore, sepsis studies generally compartmentalize the immune response to determine which immunotherapies or immunomodulators are most appropriate. Currently, Slim et al. are conducting a scoping review summarizing all immunotherapies that have been studied or are currently being studied for sepsis.[38]

For patients who have sepsis with the MALS subset, nonspecific therapies may be necessary, such as intravenous immunoglobulin (IVIG) to enhance pathogen recognition and antiapoptosis. Extracorporeal blood purification and plasma exchange may also be considered to eliminate free hemoglobin and ferritin, as free hemoglobin can induce macrophage activation. Additionally, since macrophage activation is partly mediated by inflammasomes, therapies targeting inflammasomes, such as steroids or IL-1 receptor antagonists, may be beneficial.[39]

Various therapies have been tested to enhance the immune response in sepsis with immunoparalysis. Previously trialed therapies include granulocyte–macrophage colony-stimulating factor (GM-CSF) to improve neutrophil, monocyte, and macrophage production and activity; IFN-γ to enhance leukocyte activity; IL-7 to improve lymphocyte proliferation and survival; mesenchymal stem cells to strengthen bacterial eradication, limit apoptosis, and repair cell damage; and anti-PD-L1 to reduce apoptosis and enhance T cell responses.[40,41]

Immune checkpoint inhibitors are a new therapeutic target to improve the immune response in immunoparalysis. Leukocytes have specific checkpoint proteins on their cell surface, which function to limit overactivation and maintain homeostasis. These immune checkpoint receptors are typically located on T lymphocyte membranes, where they

recognize their corresponding ligands on APCs. Expression of these receptors increases in sepsis, facilitating immunosuppression by disrupting the antimicrobial functions of leukocytes. Therapies targeting checkpoint inhibitors are expected to improve host immune responses, prevent nosocomial infections, and ultimately improve outcomes. Important immune checkpoint receptors include PD-1, PD-L1, PD-L2, CTLA-4, BTLA, LAG-3, TIM-3, and 2B4 (CD244).[42]

Immunotherapy will be increasingly utilized in the future. Before incorporating immunotherapy into sepsis management protocols, further studies are needed to determine the optimal timing of administration, whether immunotherapy should be given in combination or as monotherapy, and how to select the right patients for specific immunotherapies.

CONCLUSION

Subphenotypic classification of immune response in sepsis is a practical strategy for classifying patients with sepsis, aside from the more advanced gene expression-based classification. Each immune response group represents a distinct underlying biological process. This classification serves as a biological marker for predicting mortality and clinical outcomes, as well as for providing baseline data for future clinical trials on personalized immunotherapy for sepsis.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this study.

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