REVISTA VIRTUAL
SOCIEDAD PARAGUAYA DE MEDICINA INTERNA

REVIEW ARTICLE

Personalized immunotherapy in sepsis: Advances and challenges in therapeutic optimization

Inmunoterapia personalizada en la sepsis: avances y desafíos en la optimización terapéutica

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Cómo referenciar este artículo: Mutiz España EM, Saavedra Torres JS, Imbachi Imbachi LD, Pérez Martínez NV, Cerón López JA, Cuadrado Guevara RA, Zambrano López ED. Personalized immunotherapy in sepsis: Advances and challenges in therapeutic optimization. Rev. virtual Soc. Parag. Med. Int. 2026; 13 (1): e13132604

RESUMEN

Introducción: la sepsis representa uno de los síndromes más complejos y biológicamente heterogéneos de la medicina crítica contemporánea, caracterizado no solo por inflamación desregulada, sino también por agotamiento inmunológico simultáneo, disfunción endotelial, inmunotrombosis, lesión mitocondrial y colapso inmunometabólico. Los enfoques terapéuticos tradicionales basados exclusivamente en el control de la infección y la estabilización hemodinámica no han logrado reducir significativamente la mortalidad, debido a que no abordan la

Artículo recibido: *27 febrero 2025*
Artículo aceptado: *6 junio 2026*

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Dictamen del artículo:
https://www.revistaspmi.org.py/dictamenes/2026/5626_dictamen_2.pdf

diversidad inmunovascular dinámica presente en los pacientes sépticos. La evidencia emergente sugiere que la sepsis no debe interpretarse como un único fenotipo inflamatorio, sino como un espectro de endotipos inmunológicos y endoteliales altamente dinámicos que requieren inmunoterapia de precisión guiada por biomarcadores.

Objetivo: describir las estrategias inmunomoduladoras actuales y emergentes en sepsis, integrando desregulación inmunitaria, lesión endotelial, firmas transcriptómicas, puntos de control inmunológico, disfunción inmuno-metabólica y estratificación guiada por biomarcadores, con el fin de identificar enfoques terapéuticos personalizados capaces de mejorar los desenlaces clínicos y biológicos.

Métodos: se realizó una revisión narrativa estructurada utilizando las bases de datos PubMed, Nature, Scopus y LILACS. Se aplicaron términos MeSH y DeCS relacionados con sepsis, inmunoterapia, puntos de control inmunológico, disfunción endotelial, biomarcadores, transcriptómica, inmunometabolismo y medicina de precisión. De un total inicial de 456 estudios, se seleccionaron 54 artículos que cumplían criterios metodológicos, traslacionales y clínicos predefinidos para el análisis integrador. Se incluyeron estudios experimentales, traslacionales y clínicos que evaluaran modulación inmune, estratificación guiada por biomarcadores y mecanismos endoteliales o inmunometabólicos en sepsis.

Resultados: la sepsis mostró una marcada heterogeneidad biológica caracterizada por hiperrespuesta inflamatoria simultánea con inmunoparálisis, lesión endotelial, degradación del glicocálix, disfunción mitocondrial, colapso microcirculatorio y agotamiento inmunológico persistente. Estrategias inmunoterapéuticas como IFN-γ, GM-CSF, IL-7, timosina-α1, glucocorticoides, inhibidores de puntos de control inmunológico, inmunoglobulinas intravenosas y células madre mesenquimales demostraron efectos biológicos variables según el endotipo séptico predominante y el momento de intervención. Biomarcadores como la expresión monocítica de HLA-DR, las firmas transcriptómicas SRS1/SRS2, IL-6, IL-10, marcadores endoteliales y el perfil de puntos de control inmunológico permitieron una mejor estratificación inmunológica. Además, el modelo SIMMP–Sepsis (Síndrome Inmunometabólico Multi-orgánico Persistente Asociado a Sepsis) evidenció la persistencia de disfunción inmunometabólica e inmunovascular a largo plazo más allá de la aparente recuperación clínica.

Conclusiones: la principal limitación de la inmunoterapia en sepsis no deriva únicamente de la ineficacia terapéutica, sino de la ausencia de una estratificación biológica dinámica capaz de identificar la terapia adecuada para el endotipo inmunológico y endotelial correcto. La sepsis debe redefinirse como un trastorno inmunometabólico e inmunovascular persistente más que como un síndrome puramente inflamatorio. Las futuras estrategias de medicina de precisión requerirán integrar transcriptómica, monitoreo inmunológico, biología endo-telial, evaluación del glicocálix y perfilamiento inmunometabólico para optimizar intervenciones terapéuticas individualizadas y mejorar los desenlaces a largo plazo en pacientes críticamente enfermos.

Palabras claves: sepsis, inmunoterapia, biomarcadores, linfocitos T, células dendríticas, apoptosis

ABSTRACT

Introduction: Sepsis represents one of the most complex and biologically heterogeneous syndromes in contemporary critical care medicine, characterized not only by dysregulated inflammation, but also by simultaneous immune exhaustion,

endothelial dysfunction, immune-thrombosis, mitochondrial injury, and immunometabolic collapse. Traditional therapeutic approaches based exclusively on infection control and hemodynamic stabilization have failed to significantly reduce mortality because they do not address the dynamic immunovascular diversity of septic patients. Emerging evidence suggests that sepsis should not be interpreted as a single inflammatory phenotype, but rather as a spectrum of highly dynamic immunological and endothelial endotypes requiring biomarker-guided precision immunotherapy.

Objective: To analyze current and emerging immunomodulatory strategies in sepsis, integrating immune dysregulation, endothelial injury, transcriptomic signatures, immune checkpoints, immunometabolic dysfunction, and biomarker-guided patient stratification in order to identify personalized therapeutic approaches capable of improving clinical and biological outcomes.

Methods: A structured narrative review was conducted using PubMed, Nature, Scopus, and LILACS databases. MeSH and DeCS terms related to sepsis, immunotherapy, immune checkpoints, endothelial dysfunction, biomarkers, transcriptomics, immunometabolism, and precision medicine were applied. From an initial pool of 456 studies, 54 articles fulfilling predefined methodological, translational, and clinical relevance criteria were selected for integrative analysis. Experimental, translational, and clinical studies evaluating immune modulation, biomarker-guided stratification, and endothelial or immunometabolic mechanisms in sepsis were included.

Results: Sepsis demonstrated marked biological heterogeneity involving simultaneous hyperinflammation, immune-paralysis, endothelial injury, glycocalyx degradation, mitochondrial dysfunction, microcirculatory collapse, and persistent immune exhaustion. Immunotherapeutic strategies including IFN-γ, GM-CSF, IL-7, thymosin-α1, glucocorticoids, immune checkpoint inhibitors, intravenous immunoglobulins, and mesenchymal stem cells showed variable biological effects depending on the dominant septic endotype and timing of intervention. Biomarkers such as monocytic HLA-DR expression, transcriptomic signatures SRS1/SRS2, IL-6, IL-10, endothelial markers, and immune checkpoint profiling enabled improved immunological stratification. Additionally, the SIMMP–Sepsis model (Sepsis-Associated Persistent Multiorgan Immunometabolic Syndrome) highlighted the persistence of long-term immunometabolic and immunovascular dysfunction beyond apparent clinical recovery.

Conclusion: The principal limitation of immunotherapy in sepsis derives not only from therapeutic inefficacy, but from the absence of dynamic biological stratification capable of identifying the appropriate therapy for the appropriate immunological and endothelial endotype. Sepsis should be redefined as a persistent immunometabolic and immunovascular disorder rather than a purely inflammatory syndrome. Future precision medicine strategies will require integration of transcriptomics, immune monitoring, endothelial biology, glycocalyx assessment, and immunometabolic profiling to optimize individualized therapeutic interventions and improve long-term outcomes in critically ill patients.

Keywords: sepsis, immunotherapy, biomarkers, T lymphocytes, dendritic cells, apoptosis, sepsis-associated persistent multiorgan immunometabolic syndrome.

Abbreviations: APC: antigen-presenting cell; DIC: disseminated intravascular coagulation; GM-CSF: granulocyte-macrophage colony-stimulating factor; G-CSF: granulocyte colony-stimulating factor; HLA-DR: human leukocyte antigen - DR; IFN-γ: interferon-gamma; IL: interleukin; LAG-3: lymphocyte activation gene 3; MDRB: multidrug-resistant bacteria; NKT:

Natural Killer T; RAI: relative adrenal insufficiency; ROS: reactive oxygen species; SRS: sepsis response signature; TIM-3: T-cell immunoglobulin and mucin domain-containing protein 3; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-alpha; TIGIT: T-cell immunoreceptor with immunoglobulin and ITIM domain; UTI: urinary tract infection; VISTA: V-domain immunoglobulin suppressor of T-cell activation.

INTRODUCTION

Sepsis represents one of the most complex, dynamic, and conceptually underestimated biological syndromes in contemporary critical care medicine [1,2]. Although it has classically been defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection, this definition remains insufficient to explain the extraordinary immunological, vascular, metabolic, and micro-environmental heterogeneity observed among septic patients. Sepsis should not be interpreted as a single inflammatory phenotype nor as a linear disease process driven exclusively by cytokine storm [1,3]. Instead, it constitutes a multidimensional systemic immunovascular disorder in which hyperinflammation, immunoparalysis, immunometabolic exhaustion, mito-chondrial dysfunction, immunothrombosis, endothelial injury, and persistent tissue microenvironment remodeling coexist simultaneously and dynamically [1–6].

For decades, much of sepsis research was constructed upon reductionist models centered primarily on systemic inflammation. However, the repeated failure of therapies targeting TNF-α, IL-1, or TLR4 exposed a deeper biological problem: the incorrect assumption that all septic patients shared the same pathophysiological trajectory [3,5]. Current evidence demonstrates that sepsis evolves through highly dynamic immunological and vascular endotypes modulated by age, comorbidities, genetics, microbiome composition, metabolic status, endothelial integrity, and immunological timing [7–10]. Within this framework, the endothelium emerges as a central immunological organ. Glycocalyx degradation, loss of hemodynamic coherence, platelet activation, Weibel–Palade body exocytosis, dysregulated NETosis, and microcirculatory uncoupling transform sepsis into a state of systemic biological collapse capable of reprogramming the interaction between immunity, coagulation, and tissue architecture [11–15].

Concurrently, emerging evidence suggests that septic progression does not depend exclusively on uncontrolled inflammation, but rather on the critical convergence of persistent immune dysfunction, cellular energetic exhaustion, sustained endothelial injury, and progressive loss of biological selectivity. Prolonged lymphocyte apoptosis, reduced monocytic HLA-DR expression, expansion of immune checkpoint pathways, mitochondrial dysfunction, and persistent extracellular matrix remodeling generate an adaptively dysfunctional immunovascular microenvironment that may persist even after apparent clinical recovery [16–20]. Under this perspective, immunotherapy in sepsis can no longer rely on universal therapeutic protocols. The true challenge lies in identifying the precise immunological moment, the dominant biological endotype, and the degree of immunovascular involvement in each individual patient. The integration of transcriptomics, endothelial biomarkers, immune checkpoint profiling, metabolomics, and dynamic glycocalyx monitoring will likely redefine the future of precision critical care in sepsis [21–24].

METHODOLOGY

A literature review was conducted using the PubMed, Nature, and Scopus databases, applying the MeSH terms "sepsis OR

immune response OR immunotherapy AND biomarkers AND precision medicine." Filters were applied to restrict the search to full-text articles in English or Spanish, yielding a total of 456 studies. Duplicates, narrative reviews, and letters to the editor were excluded. A complementary search was performed in LILACS using the DeCS terms "sepsis OR immunotherapy OR biomarkers OR immune modulation OR precision medicine," identifying 12 additional articles, which were assessed based on predefined inclusion and exclusion criteria.

The analysis included original research articles and systematic reviews in English or Spanish, human studies providing clinical evidence on immunomodulatory strategies in sepsis, investigations examining immune response biomarkers and their role in patient stratification, and studies evaluating immunomodulatory therapies such as GM-CSF, IFN-γ, and TIM-3, LAG-3, and TIGIT inhibitors. Additionally, animal and in vitro studies contributing relevant insights into the immunological mechanisms and therapeutic potential of these strategies were included.

Only full-text publications from indexed databases were considered. Exclusion criteria encompassed duplicate studies, narrative reviews, letters to the editor, expert opinions without systematic analysis, articles that did not directly address immunomodulatory strategies in sepsis, studies with non-representative populations (patients with primary or secondary immunodeficiencies), and publications lacking detailed methodology or clinically relevant results. Ultimately, 54 articles meeting the established methodological and quality criteria were selected and thoroughly analysed for this review.

RESULTS

Immune Dysregulation in Sepsis

Immune dysregulation in sepsis represents a dynamic and multidimensional biological process characterized not only by excessive inflammation, but also by profound alterations in immune surveillance, endothelial integrity, cellular metabolism, and tissue homeostasis [8,9]. Rather than evolving through isolated inflammatory phases, sepsis involves the simultaneous coexistence of hyperinflammation, immunoparalysis, thromboinflammation, mitochondrial dysfunction, and progressive immunovascular collapse. Early activation of innate immune pathways through pattern-recognition receptors, particularly Toll-like receptors such as TLR4, initiates a coordinated inflammatory cascade involving TNF-α, IL-1β, IL-6, complement activation, platelet signaling, and neutrophil extracellular trap formation [9,10]. Although initially protective, sustained activation of these pathways promotes diffuse endothelial injury, glycocalyx degradation, microvascular dysfunction, and loss of hemodynamic coherence, ultimately amplifying tissue hypoxia and organ dysfunction [10,11].

Concurrently, sepsis induces profound immune cellular reprogramming. Massive apoptosis of lymphocytes, dendritic cells, and antigen-presenting cells is accompanied by reduced monocytic HLA-DR expression, persistent T-cell exhaustion, impaired interferon signaling, dysfunctional NK-cell activity, and maladaptive macrophage polarization toward immunosuppressive phenotypes [11,12]. These alterations do not represent passive immune failure, but rather an adaptively dysfunctional state in which immune cells remain metabolically active while operating under persistent inhibitory signaling. Expansion of immune checkpoint pathways, including PD-1, TIM-3, LAG-3, and TIGIT, further contributes to defective

pathogen clearance and increased susceptibility to secondary bacterial, viral, and fungal infections [12,13].

Current evidence suggests that sepsis should not be interpreted as a homogeneous inflammatory syndrome, but as a biologically heterogeneous immunovascular disorder with highly dynamic trajectories over time. Clinical manifestations such as fever, vasoplegia, tachycardia, and cytokine amplification may coexist with profound immunosuppression, endothelial activation, and immunometabolic exhaustion from the earliest stages of disease [13,14]. Consequently, understanding sepsis requires integration of immune monitoring, endothelial biology, transcriptomic profiling, and metabolic assessment to identify dominant biological endotypes capable of guiding precision immunotherapeutic strategies in critically ill patients [14].

Immunotherapy in sepsis: Current challenges

Immunotherapy in sepsis emerged from the recognition that septic progression cannot be explained exclusively by uncontrolled inflammation, but rather by the coexistence of hyperinflammation, endothelial injury, immune exhaustion, immunometabolic dysfunction, and progressive loss of biological homeostasis [15–17]. Consequently, the therapeutic objective is not indiscriminate suppression of inflammation, but restoration of immunological competence while preserving endothelial integrity and pathogen clearance capacity. This distinction is critical because many early therapeutic strategies failed after assuming that all septic patients shared a similar inflammatory trajectory. Current evidence demonstrates that septic patients evolve through highly heterogeneous immunological endotypes characterized by distinct inflammatory, endothelial, and metabolic profiles [8,9,18,19].

Among immunostimulatory approaches, interferon-gamma (IFN-γ), granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF) demonstrated the ability to partially restore monocytic activation, antigen presentation, and macrophage responsiveness, particularly in patients with reduced HLA-DR expression and features of immunoparalysis [8,20–23]. However, clinical efficacy remained inconsistent because therapeutic response depended strongly on age, baseline immune reserve, comorbidities, timing of intervention, and severity of endothelial dysfunction. These findings reinforced the concept that successful immunotherapy in sepsis requires biomarker-guided stratification rather than universal treatment protocols [8,19,23,24].

Interleukin-1 receptor antagonism represented one of the earliest attempts at targeted immunomodulation. Initial trials with anakinra failed to demonstrate global mortality reduction, largely because treatment was applied to heterogeneous septic populations without biological stratification. Subsequent analyses identified a subgroup of patients with hepatobiliary dysfunction, macrophage activation-like profiles, and disseminated intravascular coagulation who experienced improved survival following IL-1 blockade [25–27]. These observations suggest that IL-1-driven hyperinflammation may dominate only specific septic endotypes rather than the syndrome as a whole [25,26].

Tumor necrosis factor-alpha (TNF-α) inhibition produced similar translational limitations. Although monoclonal antibodies against TNF-α improved survival in experimental models by attenuating early cytokine amplification and endothelial activation, human studies generated conflicting results [28–30]. Importantly,

elevated IL-6 concentrations appeared to identify patients with persistent cytokine-driven inflammation who potentially benefited from anti-TNF strategies. This interaction highlights the biological interdependence between TNF-α and IL-6 signaling pathways, where TNF-α acts as an upstream inflammatory amplifier capable of sustaining IL-6-mediated endothelial injury, coagulation activation, and systemic inflammatory propagation [28,29].

Toll-like receptor 4 (TLR4) blockade also demonstrated promising preclinical effects because lipopolysaccharide-mediated TLR4 activation plays a dominant role in Gram-negative sepsis, endothelial activation, and thromboinflammation [8,31–33]. Agents such as eritoran and TAK-242 attenuated cytokine release, microvascular injury, and organ dysfunction in experimental models. Nevertheless, clinical trials failed to reproduce these benefits, partially because many enrolled patients lacked dominant TLR4-driven phenotypes or were already in advanced immunosuppressive stages at the time of intervention. Collectively, these findings demonstrate that the principal limitation of immunotherapy in sepsis is not necessarily therapeutic inefficacy, but the persistent absence of dynamic immune, endothelial, and immunometabolic stratification capable of identifying the right therapy for the right biological endotype at the appropriate immunological moment [31–33].

Glucocorticoids in sepsis

The use of glucocorticoids in sepsis represents one of the clearest examples of how biological heterogeneity profoundly determines therapeutic response in critical care medicine [34]. Early clinical trials conducted in patients with severe sepsis and septic shock initially reported apparent reductions in mortality with high-dose corticosteroid therapy [35].

However, subsequent investigations demonstrated that administration of elevated glucocorticoid doses promoted profound immunosuppression, increased secondary infections, viral reactivation, metabolic dysfunction, critical illness myopathy, and significantly higher mortality rates [36,37]. These findings fundamentally changed the pathophysiological interpretation of steroid therapy in sepsis, demonstrating that septic patients cannot be managed through indiscriminate anti-inflammatory strategies universally applied across biologically distinct populations [34–37].

Subsequent studies evaluated low- and moderate-dose corticosteroid regimens aimed at restoring vascular responsiveness to catecholamines, attenuating excessive inflammatory signaling, and improving hemodynamic stability during septic shock [34,36]. Although survival outcomes remained inconsistent across different cohorts, the combination of hydrocortisone and fludrocortisone demonstrated significant reductions in 90-day mortality among patients with refractory septic shock, suggesting that glucocorticoid efficacy depends more on the host's immunoendocrine context than on corticosteroid administration alone [35,37].

Current evidence indicates that approximately 25% to 60% of septic patients develop relative adrenal insufficiency (RAI), characterized by impaired hypothalamic–pituitary–adrenal axis adaptation during systemic inflammatory stress [8,35]. Experimental models demonstrated that glucocorticoids may restore vascular stability, improve catecholamine responsiveness, and attenuate inflammatory injury in the presence of RAI [37]. In contrast, administration in patients without adrenal dysfunction may amplify lymphocyte apoptosis, immunoparalysis, impaired microbial clearance, and persistent immune exhaustion [8,35,37].

The biological complexity of glucocorticoid response became even more evident following the identification of transcriptomic sepsis response signatures known as SRS1 and SRS2, derived from peripheral blood leukocyte gene-expression profiling in septic patients [38,39].

The SRS1 phenotype is characterized by profound immune dysregulation, adaptive immune suppression, persistent lymphocyte exhaustion, reduced monocytic HLA-DR expression, and overexpression of genes associated with sustained inflammation, tissue injury, endothelial dysfunction, and multiple organ failure [8,40]. These patients exhibit increased susceptibility to secondary infections and markedly worse clinical outcomes [8,38]. In contrast, SRS2 reflects a comparatively more regulated immune profile with better preservation of immune competence, lower inflammatory intensity, and greater biological recovery capacity [39,40].

Importantly, transcriptomic analyses demonstrated that patients with the SRS2 phenotype experienced increased mortality when treated with corticosteroids, suggesting that pharmacologically induced immunosuppression may become deleterious in biologically less inflammatory endotypes or in patients with preserved immune reserve [38–40]. These findings reinforce the concept that glucocorticoids should not be interpreted merely as anti-inflammatory agents, but rather as immunoendocrine modulators whose biological effects depend critically on host endotype, transcriptomic profile, immunovascular integrity, and temporal immune trajectory [8,38].

New immunotherapeutic strategies in sepsis

The development of novel immunotherapeutic strategies in sepsis emerged from the recognition that septic progression is not driven exclusively by excessive inflammation, but also by profound immune exhaustion, endothelial dysfunction, immunometabolic collapse, and persistent failure of cellular adaptive mechanisms [8,41]. Consequently, modern immunotherapy no longer focuses solely on suppressing inflammatory cytokines, but rather on selectively restoring immune competence according to the biological endotype and temporal trajectory of each septic patient [42]. This concept is particularly relevant because multiple therapeutic failures in sepsis resulted from the application of universal interventions across highly heterogeneous and biologically dynamic immune states [43].

Among immunostimulatory therapies, granulocyte–macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) demonstrated the capacity to partially reverse monocytic hyporesponsiveness and improve antigen presentation through increased monocytic HLA-DR expression [8,41]. From a cellular perspective, these agents enhance macrophage activation, neutrophil maturation, phagocytic activity, and partial restoration of innate immune signaling, potentially improving microbial clearance during immunoparalytic stages of sepsis [42,43]. In preterm neonates with sepsis-associated neutropenia, recombinant G-CSF accelerated leukocyte recovery and reduced infection-related complications associated with persistent neutropenia [44].

However, subsequent meta-analyses demonstrated that although these therapies improve infection resolution and selected immunological parameters, they do not consistently reduce overall mortality in patients with severe sepsis or septic shock [41–44]. These findings suggest that restoration of isolated immune functions may be biologically insufficient when endothelial injury, mitochondrial dysfunction, and systemic immunometabolic exhaustion remain unresolved [8].

Thymosin-α1 (Tα1), an endogenous thymic peptide involved in T-cell maturation and immune regulation, demonstrated promising immunomodulatory effects by increasing monocytic HLA-DR expression, restoring lymphocyte activity, and reducing secondary infections [45]. Combined administration of Tα1 with ulinastatin (UTI) was associated with lower 28-day and 90-day mortality in selected septic populations, suggesting a favorable biological interaction between inflammatory modulation and immune restoration [46]. Similarly, interferon-gamma (IFN-γ) demonstrated phase-dependent biological effects influenced by the host inflammatory state [8].

Although potentially deleterious during early hyperinflammatory stages, IFN-γ may reverse post-sepsis immunoparalysis by restoring macrophage activation, interferon signaling, and antimicrobial responsiveness in critically immunosuppressed patients [45,46]. Interleukin-7 (IL-7) also emerged as a relevant immunorestorative therapy because of its ability to reverse profound lymphopenia, preserve T-cell survival, and restore adaptive immune competence in both sepsis and severe COVID-19 [46].

More recently, therapeutic interest has shifted toward immune checkpoint pathways as central mediators of persistent immune exhaustion in sepsis [8]. TIM-3 overexpression was associated with increased mortality, impaired T-cell function, and greater susceptibility to Gram-positive infections [47–49]. Experimental TIM-3 inhibition reduced Natural Killer T-cell apoptosis, modulated NF-κB signaling, and partially restored immune responsiveness during septic progression [50]. Similarly, LAG-3 functions as a potent inhibitory receptor suppressing lymphocyte proliferation and adaptive immune activation [51]. Genetic polymorphisms involving LAG-3 influenced sepsis mortality, while receptor blockade or genetic deletion improved immune responsiveness and reduced sepsis-induced immune dysfunction in experimental models [52–54].

Comparable findings were observed with TIGIT and VISTA, co-inhibitory molecules strongly associated with persistent immunosuppression, lymphocyte exhaustion, and defective bacterial clearance in sepsis [8]. Experimental TIGIT blockade restored T-cell activity and improved survival in murine sepsis models, whereas VISTA inhibition reduced lymphocyte apoptosis, attenuated inflammatory cytokine release, and improved systemic microbial control [8].

Other emerging strategies include IgM-enriched intravenous immunoglobulins (IVIgGM) and mesenchymal stem cells (MSC). Reduced immunoglobulin concentrations have been associated with increased severity and mortality in sepsis [8], and several studies demonstrated that IVIgGM may reduce duration of mechanical ventilation and infection severity in critically ill patients [8]. Nevertheless, the Surviving Sepsis Campaign currently does not recommend routine IVIgGM administration because of insufficient robust and consistent high-quality evidence [8]. Conversely, MSC demonstrated immunomodulatory, endothelial-protective, mitochondrial, and regenerative properties in experimental sepsis models, reducing systemic inflammation, endothelial injury, and multiorgan dysfunction [8].

Immune biomarkers and monitoring in sepsis

Immune monitoring and biomarker-guided approaches have emerged as central components of precision medicine in sepsis because septic progression is characterized by highly dynamic and biologically heterogeneous immune trajectories rather than uniform inflammatory responses [8]. Contemporary evidence demonstrates that

sepsis evolves through simultaneous and overlapping states of hyperinflammation, immune exhaustion, endothelial dysfunction, immunometabolic collapse, and persistent cellular stress, making static therapeutic strategies biologically insufficient [1,2]. Consequently, identification of immune profiles and dominant biological endotypes may allow targeted interventions capable of reducing secondary infections, organ dysfunction, prolonged critical illness, and mortality [8].

Among currently investigated biomarkers, monocytic HLA-DR expression remains one of the most clinically relevant indicators of immune competence in septic patients because reduced HLA-DR levels correlate with monocyte deactivation, impaired antigen presentation, secondary infections, and worse prognosis [3,4]. Likewise, transcriptomic profiling has enabled identification of genomic sepsis response signatures such as SRS1 and SRS2, which reflect distinct immunobiological trajectories and differential responses to immunomodulatory therapies [8,9].

The SRS1 phenotype is associated with profound immune dysregulation, persistent inflammation, adaptive immune suppression, and increased mortality, whereas SRS2 reflects comparatively preserved immune regulation and greater biological recovery capacity [8,9]. These findings reinforce the concept that sepsis should not be interpreted as a single inflammatory phenotype, but rather as a spectrum of immunovascular endotypes requiring individualized therapeutic modulation [8,9].

Additional biomarkers involving cytokine profiles, immune checkpoint expression, endothelial injury markers, metabolomic signatures, and glycocalyx degradation products have also demonstrated potential utility for immune stratification and biological monitoring during septic progression [5,6]. Increased expression of checkpoints such as TIM-3, LAG-3, TIGIT, and PD-1 correlates with lymphocyte exhaustion and persistent immunosuppression, potentially identifying patients who may benefit from selective immune checkpoint modulation [5]. Simultaneously, biomarkers reflecting endothelial dysfunction and microcirculatory injury may provide critical information regarding progression toward immunovascular collapse and multiorgan dysfunction [6,7].

Although immunomodulatory therapies including GM-CSF, IFN-γ, IL-7, and immune checkpoint inhibitors demonstrated promising immunological effects in experimental and translational studies, clinical outcomes remain inconsistent because therapeutic interventions are frequently applied without dynamic biological stratification [3–7]. Therefore, the development of integrated biomarker panels, rapid bedside immune monitoring systems, transcriptomic platforms, and endothelial assessment tools will likely redefine future precision immunotherapy models in sepsis by enabling identification of the right therapy for the right biological endotype at the appropriate immunological moment [10,11].

Traditional biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) remain among the most widely used tools for sepsis monitoring because they provide rapid and clinically accessible information regarding systemic inflammatory activity and response to antimicrobial therapy [8].

CRP reflects hepatic acute-phase activation mediated predominantly by IL-6 signaling, whereas procalcitonin demonstrates greater specificity for bacterial infection and may help guide antibiotic de-escalation strategies in critically ill patients [9,10]. However, both biomarkers present important biological limitations because they do not adequately differentiate hyperinflammatory states from immu-

noparalysis, endothelial dysfunction, or immunometabolic exhaustion [11].

In contrast, cytokines such as IL-6, TNF-α, and IL-10 provide deeper insight into dynamic immune trajectories and may better reflect the coexistence of inflammation and immune suppression during septic progression [8]. Elevated IL-6 concentrations correlate with disease severity, endothelial injury, and mortality, while persistent IL-10 elevation is associated with adaptive immune suppression and secondary infections [10,11]. TNF-α, despite being a central mediator of early inflammatory amplification, demonstrates limited utility as an isolated monitoring biomarker because of its rapid kinetic variability and short plasma half-life [8].

Consequently, contemporary evidence suggests that isolated biomarkers are biologically insufficient for precision monitoring in sepsis, reinforcing the need for integrated biomarker panels combining inflammatory mediators, endothelial markers, immune checkpoints, transcriptomics, and monocytic HLA-DR expression to accurately characterize the dominant septic endotype and guide personalized immunotherapeutic interventions [8–11] (Table 1).

Persistent Immunometabolic Sepsis

Beyond classical inflammation and conventional immunoparalysis, one of the most underrecognized dimensions of sepsis is the persistence of multisystem immunometabolic disruption after the apparent clinical resolution of infection [55,56]. Traditional paradigms continue to interpret sepsis as an acute inflammatory event restricted to the period of hemodynamic instability and intensive care support [57,58]. However, contemporary evidence increasingly demonstrates that many survivors evolve toward a persistent biological state characterized by residual inflammation, immune exhaustion, endothelial dysfunction, mitochondrial injury, maladaptive metabolic reprogramming, and chronic tissue vulnerability. Within this context, the SIMMP–Sepsis model (Sepsis-Associated Persistent Multiorgan Immunometabolic Syndrome) emerges as an integrative conceptual framework capable of connecting the acute septic response with the long-term immunological, vascular, metabolic, and functional consequences that frequently persist long after apparent recovery [55,56].

The SIMMP–Sepsis model proposes that sepsis does not conclude with microbiological control or circulatory stabilization. Instead, the septic insult initiates a sustained process of cellular and molecular reconfiguration involving innate immunity, adaptive immune regulation, endothelial integrity, mitochondrial bioenergetics, neuroimmune signaling, and tissue repair pathways [55,56]. During the acute phase, pathogen-associated and damage-associated molecular patterns activate Toll-like receptors, inflammasome pathways, oxidative stress cascades, NETosis, and immunothrombotic signaling. Although initially protective, persistent activation of these pathways promotes endothelial collapse, glycocalyx degradation, mitochondrial fragmentation, and progressive loss of biological coherence across multiple organ systems [55,56].

The critical transition toward persistent immunometabolic dysfunction occurs when these adaptive responses fail to fully return to physiological homeostasis. Persistently reduced monocytic HLA-DR expression, chronic T-cell exhaustion with overexpression of PD-1 and BTLA, dysfunctional neutrophil phenotypes enriched in PD-L1, expansion of regulatory T cells, and sustained anti-inflammatory cytokine signaling generate a hybrid biological environment in which chronic low-grade inflammation coexists simultaneously with adaptive immune

suppression. Under these conditions, the immune system remains metabolically active yet functionally inefficient, creating vulnerability to secondary infections, impaired tissue repair, and progressive physiological decline [55,56].

From a molecular perspective, SIMMP–Sepsis integrates immunometabolism and epigenetic reprogramming into a unified biological model. Metabolites such as succinate, lactate, and fumarate function not merely as energetic intermediates, but also as transcriptional regulators capable of modifying histone signaling through lactylation and methylation pathways. These alterations sustain maladaptive inflammatory memory, persistent immune activation, and defective resolution programs. Simultaneously, mitochondrial DNA release and chronic activation of the cGAS–STING pathway perpetuate sterile inflammatory signaling, dendritic cell dysfunction, and progressive immune exhaustion. At the vascular level, incomplete restoration of the endothelial glycocalyx maintains angiopoietin-2 elevation, endothelial activation, microcirculatory incoherence, and persistent subclinical immunothrombosis [57,58].

Clinically, this framework explains why many sepsis survivors develop chronic fatigue, accelerated frailty, sarcopenia, cognitive dysfunction, recurrent infections, dysautonomia, cardiovascular vulnerability, fibrosis, and long-term functional deterioration even years after the initial septic event. SIMMP–Sepsis therefore redefines sepsis not as a transient inflammatory syndrome, but as a persistent immunometabolic and immunovascular disorder capable of accelerating systemic biological aging and multisystem decline [57,58]. Under this perspective, survival no longer represents the endpoint of disease, but rather the beginning of a prolonged phase of biological recovery requiring dynamic immune monitoring, endothelial assessment, metabolic characterization, and precision therapeutic strategies aimed at restoring long-term physiological resilience [55,56].

Immunoadaptation Beyond Sepsis

The relationship between sepsis and immunosenescence has historically been interpreted as a direct consequence of irreversible immune exhaustion induced by severe systemic inflammation. However, this explanation is currently insufficient to describe the biological complexity observed in sepsis survivors and in patients exposed to persistent inflammatory stress [59,60].

The classical paradigm of immunosenescence originated from experimental observations of replicative cellular limitation and age-associated progressive decline in immune function [55,56]. This concept was subsequently extrapolated to severe inflammatory diseases under the assumption that prolonged exposure to immune stress inevitably culminates in terminal cellular dysfunction and irreversible biological collapse [56,57]. Nevertheless, contemporary molecular, immunometabolic, and transcriptomic evidence demonstrates that immune cells exposed to sustained inflammatory signaling do not necessarily enter a state of complete biological inactivity. Instead, they undergo dynamic programs of functional adaptive reprogramming involving metabolic remodeling, epigenetic modification, mitochondrial stress responses, and persistent alterations in intercellular signaling networks [59,60].

In sepsis, persistent lymphocyte exhaustion, suppression of monocytic HLA-DR expression, altered interferon signaling, expansion of immune checkpoints, and maladaptive myeloid polarization should not be interpreted merely as passive immune collapse. Rather, these alterations represent a state of maladaptive immunoadaptation in which immune cells

remain metabolically active while reorganizing their biological priorities toward immediate survival, inflammatory tolerance, and preservation of tissue integrity under extreme physiological stress [55,56]. This distinction is clinically and mechanistically critical because the concept of immunosenescence may falsely suggest a biologically inert immune system, whereas persistent post-septic immune dysfunction is characterized by intense transcriptional, metabolic, and epigenetic activity [59,60].

Sepsis generates an environment of profound systemic stress in which immune, endothelial, stromal, and metabolic systems activate compensatory programs aimed at preserving cellular viability during hypoxia, oxidative injury, mitochondrial dysfunction, and sustained inflammatory exposure (55,56). During this process, signaling pathways including NF-κB, STAT3, HIF-1α, cGAS–STING, and IL-6-associated inflammatory cascades remain persistently activated, supporting tissue repair, bioenergetic maintenance, and cellular survival despite ongoing systemic injury. However, prolonged maintenance of these adaptive programs imposes a progressive biological cost. Immune regulation gradually prioritizes inflammatory tolerance and structural preservation over genomic surveillance precision, cytotoxic selectivity, and elimination of aberrant cellular clones [59,60].

Within this context, persistent immunoadaptive mechanisms emerge through sustained overexpression of PD-1, PD-L1, TIM-3, TIGIT, LAG-3, and CTLA-4, all of which reduce antigen-directed cytotoxic activity and impair effective immune surveillance [59,60].

Simultaneously, chronic endothelial activation, glycocalyx degradation, extracellular matrix remodeling, and extracellular vesicle signaling generate biologically permissive tissue micro-environments characterized by chronic low-grade inflammation, persistent myeloid recruitment, and microvascular dysfunction [55,56]. Under these conditions, tissues do not become biologically inactive; instead, they remain highly active while operating under maladaptive regulatory hierarchies optimized for short-term survival rather than long-term physiological fidelity [59,60].

This framework provides a more coherent explanation for why many sepsis survivors subsequently develop accelerated frailty, sarcopenia, recurrent infections, neurocognitive decline, cardiovascular dysfunction, organ fibrosis, and potentially increased oncologic vulnerability years after the initial septic insult [59,60].

Sepsis itself should not be interpreted as a deterministic cause of cancer. However, persistent post-inflammatory immu-noadaptation may reduce immune surveillance capacity and facilitate the persistence of pre-existing oncogenic alterations, dormant transformed cells, or accumulated genomic instability [59,60].

Consequently, isolated immunosenescence does not adequately explain post-septic biology. The concept of immunoadaptation more accurately describes an immune system that remains dynamic, metabolically active, and functionally reorganized under sustained inflammatory pressure [59,60].

This conceptual transition fundamentally redefines sepsis not as a transient inflammatory event, but as a persistent immunometabolic and immunovascular syndrome capable of profoundly remodeling immune, endothelial, stromal, and metabolic physiology long after apparent clinical recovery [59,60] (Figure 1).

Discussion

The contemporary understanding of sepsis has undergone a profound conceptual

transformation, shifting from a reductionist inflammatory paradigm toward a multidimensional immunovascular and immunometabolic model.

The evidence analyzed throughout this review demonstrates that sepsis cannot be interpreted as a homogeneous syndrome driven exclusively by cytokine amplification, but rather as a biologically heterogeneous disorder involving simultaneous hyperinflammation, immune exhaustion, endothelial dysfunction, mitochondrial injury, immunothrombosis, and persistent metabolic reprogramming. This biological complexity largely explains the repeated failure of universal immunomodulatory therapies applied without immune or endothelial stratification.

One of the most relevant findings is that immune dysfunction in sepsis does not represent simple immune collapse, but a dynamic process of maladaptive immunoadaptation. Persistent reduction of monocytic HLA-DR expression, expansion of inhibitory checkpoints such as PD-1, TIM-3, LAG-3, and TIGIT, dysfunctional interferon signaling, and sustained endothelial activation reveal that septic progression involves active biological reorganization rather than passive immunological failure. Under these conditions, immune cells remain metabolically active but functionally inefficient, favoring secondary infections, defective tissue repair, and progressive physiological deterioration.

The review also highlights the critical role of endothelial biology in septic progression. Glycocalyx degradation, microcirculatory incoherence, platelet activation, Weibel–Palade body exocytosis, and persistent immunothrombosis establish the endothelium as a central regulator of organ dysfunction and systemic biological instability. Consequently, future immunotherapeutic strategies cannot focus solely on inflammatory cytokines while ignoring vascular and metabolic integrity.

Similarly, the identification of transcriptomic signatures such as SRS1 and SRS2, together with biomarkers including HLA-DR, IL-6, IL-10, and immune checkpoint expression, reinforces the necessity of precision medicine approaches in critical care. The variable efficacy observed with glucocorticoids, GM-CSF, IFN-γ, IL-7, checkpoint inhibitors, and mesenchymal stem cells demonstrates that therapeutic success depends fundamentally on biological timing, immune reserve, endothelial status, and dominant septic endotype.

Finally, the SIMMP–Sepsis framework expands the understanding of sepsis beyond acute mortality by proposing that septic injury may induce persistent immunometabolic and immunovascular remodeling long after apparent clinical recovery. This perspective provides a coherent explanation for chronic frailty, sarcopenia, recurrent infections, neurocognitive decline, and long-term systemic vulnerability observed in survivors. Collectively, these findings support the need to redefine sepsis as a persistent multisystem biological disorder requiring dynamic monitoring, biomarker-guided stratification, and individualized immunotherapeutic interventions rather than uniform therapeutic protocols.

CONCLUSION

Sepsis should no longer be interpreted as an isolated inflammatory syndrome mediated exclusively by cytokine dysregulation. Contemporary evidence demonstrates that sepsis constitutes a highly heterogeneous immunovascular and immunometabolic disorder involving simultaneous interactions between hyperinflammation, adaptive immune exhaustion, endothelial dysfunction,

immunothrombosis, mitochondrial injury, microcirculatory failure, and persistent cellular metabolic reprogramming. This biological complexity explains the repeated failure of universal therapeutic strategies despite major advances in antimicrobial therapy, hemodynamic support, and intensive care management.

Current immunotherapeutic approaches, including glucocorticoids, GM-CSF, IFN-γ, IL-7, immune checkpoint inhibitors, mesenchymal stem cells, and biomarker-guided interventions, indicate that therapeutic efficacy depends fundamentally on precise biological stratification.

Variables such as immune reserve, endothelial integrity, transcriptomic profile, glycocalyx damage, metabolic status, and temporal immune trajectory directly influence treatment response. Consequently, the principal limitation of immunotherapy in sepsis is not merely the absence of effective drugs, but the inability to identify the dominant biological endotype and the appropriate immunological moment for intervention.

The integration of transcriptomics, endothelial biomarkers, immune monitoring, glycocalyx assessment, and immunometabolic profiling will likely redefine precision medicine in sepsis. Biomarkers such as monocytic HLA-DR expression, IL-6, IL-10, transcriptomic signatures, and immune checkpoint profiling provide clinically relevant tools for identifying distinct septic trajectories and optimizing individualized therapeutic decisions.

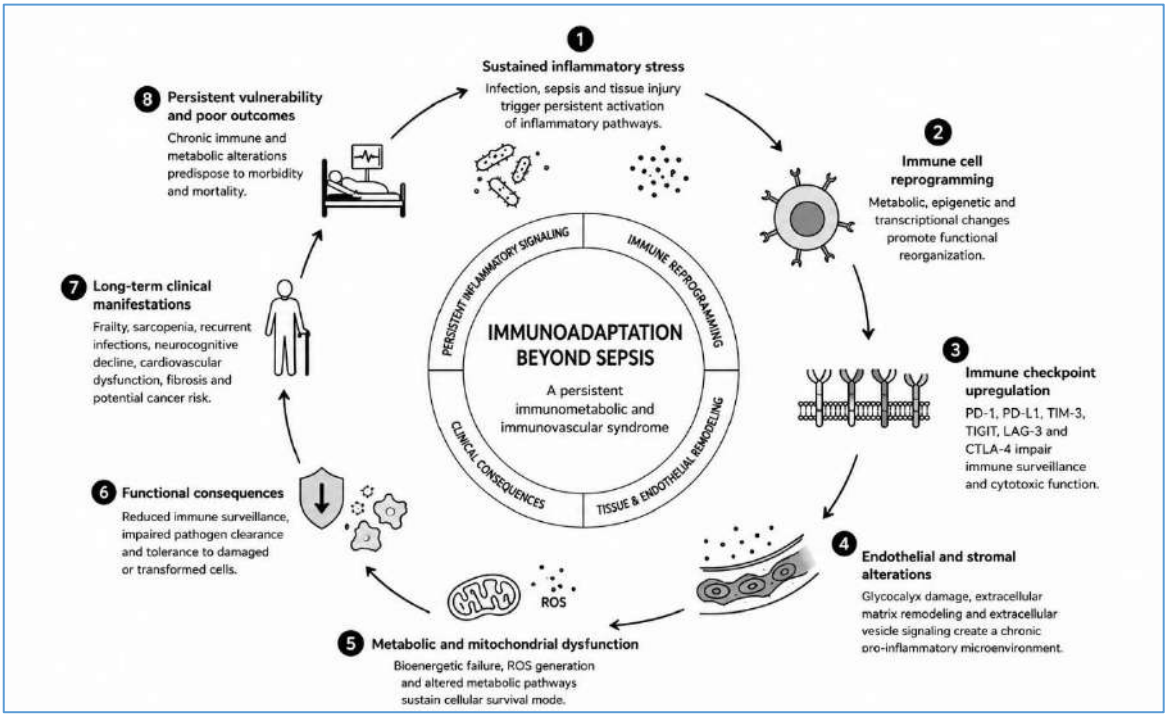

Figure 1. Conceptual schematic of persistent immunoadaptation beyond sepsis. The diagram illustrates the transition from acute inflammatory stress toward chronic immunometabolic and immunovascular remodeling, integrating immune reprogramming, endothelial dysfunction, mitochondrial injury, and long-term multisystem consequences [1,4,5,47,48]. Original figure developed by the authors with conceptual and graphical assistance from artificial intelligence tools. All scientific interpretation, organization, and intellectual content correspond exclusively to the authors.

Furthermore, concepts such as persistent immunoadaptation and SIMMP–Sepsis expand the current understanding of sepsis beyond acute mortality, recognizing septic injury as a process capable of inducing prolonged multisystem biological remodeling involving immune, endothelial, stromal, and metabolic networks. Persistent endothelial activation, maladaptive immune reprogramming, mitochondrial dysfunction, and chronic inflammatory signaling may contribute to long-term frailty, recurrent infections, neurocognitive decline, sarcopenia, fibrosis, and progressive physiological deterioration in survivors.

Future strategies in sepsis management must therefore move beyond generalized protocols and transition toward dynamic precision medicine models capable of restoring immunological competence, endothelial stability, metabolic resilience, and long-term biological recovery.

DECLARATIONS

Conflict of Interest

The authors declare that there are no financial, academic, institutional, or commercial conflicts of interest related to the content of this article. The work was conducted independently within the framework of academic and scientific research activities.

Funding

The authors declare that this research received no external funding from public, private, or commercial institutions. The manuscript was developed using the authors' own academic and research resources.

Table 1. This table summarizes key insights on sepsis, emphasizing the importance of personalized treatment and continuous biomarker monitoring in clinical practice. [2,5,55,56,58]

Key insights on sepsis: Immunological response and clinical implications		**Clinical Implications**
Definition of sepsis	Dysregulated immune response to infection that can lead to organ dysfunction.	Early recognition for timely intervention.
Immunological phases	1. Exacerbated inflammation 2. Progressive immunosuppression	Changes in patient management according to the phase of the disease.
Key biomarkers	- HLA-DR: Indicator of immune function - Genomic Signature SRS: Patient stratification (SRS1 and SRS2)	Improvement in treatment personalization.
Immunomodulatory strategies	- IFN-γ: Enhances macrophage function - GM-CSF: Restores immune response	Potential to restore immunity in patients.
Use of glucocorticoids	High doses may increase mortality; low doses do not improve survival, but combinations have benefits.	Careful evaluation of use in sepsis treatment is required.
Immune checkpoint inhibitors	- TIM-3: Improves survival by regulating NK cell apoptosis - LAG-3: Enhances immune response	New therapeutic perspectives in sepsis.
Novel therapeutic strategies	- Tα1: Increases HLA-DR, improves prognosis - Mesenchymal Stem Cells: Reduce inflammation and organ damage	Innovations in treatments to enhance recovery.
Challenges of immunotherapy	Heterogeneity among patients complicates universal treatments; a personalized approach is needed.	Identification of subgroups for more effective interventions.
Monitoring of biomarkers	Identification of immune profiles allows for specific interventions and prevention of secondary infections.	Proactive strategies in sepsis management.

(Original elaboration by the authors, based on a comprehensive review of the literature cited in the manuscript).

Data Availability

The data analyzed in this study were obtained exclusively from previously published scientific literature, indexed articles, and academic sources available in recognized biomedical databases.

Use of Artificial Intelligence

The authors declare that artificial intelligence tools were used exclusively as partial support for linguistic correction, academic writing refinement, structural organization, and grammatical optimization of selected sections of the manuscript. Scientific conceptualization, patho-physiological interpretation, mechanistic integration, critical analysis of the evidence, development of hypotheses, creation of conceptual figures, and final manuscript preparation were conducted entirely under human intellectual direction by the authors.

Publication Statement

The authors declare that this manuscript is original, has not been previously published, and is not currently under simultaneous consideration by another scientific journal, congress, academic platform, or dissemination medium.

Ethical Considerations

As this study corresponds to a narrative review based exclusively on previously published scientific literature, approval by an ethics committee and informed consent were not required, in accordance with international regulations for research without direct intervention in human subjects.

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