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Personalized Therapeutic Strategies in Sepsis and Septic Shock: Integrating Biomarkers, Immune Phenotypes, and Targeted Interventions

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ABSTRACT

Sepsis remains a major global health challenge and is characterized by a highly heterogeneous and dysregulated host response to infection that can lead to life-threatening organ dysfunction and septic shock. Despite advances in critical care management, clinical outcomes remain poor in a significant proportion of patients, largely due to the biological and clinical heterogeneity of the syndrome. In recent years, increasing attention has been directed toward precision medicine approaches aimed at improving patient stratification and guiding individualized therapeutic strategies. This review summarizes current evidence on the classification of sepsis into distinct phenotypes and endotypes based on clinical characteristics, immune response profiles, and biomarker signatures. Particular emphasis is placed on the spectrum of immune dysregulation ranging from hyperinflammatory states to immunosuppressive phenotypes and the implications of these patterns for targeted therapeutic interventions. Emerging rescue strategies for refractory septic shock, including extracorporeal life support modalities such as extracorporeal membrane oxygenation, hemoadsorption techniques, immunomodulatory therapies, and other phenotype-directed interventions, are also discussed. In addition, advances in biomarker-guided stratification and translational insights into the molecular mechanisms underlying sepsis pathophysiology are highlighted. Collectively, these developments underscore the potential of precision medicine frameworks to improve the identification of clinically relevant patient subgroups and to optimize therapeutic decision-making. Future research focusing on validated biomarkers, robust phenotyping strategies, and well-designed clinical trials will be essential to translate these concepts into improved clinical outcomes for patients with sepsis and septic shock.

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Introduction

Sepsis, as defined by the current international consensus, represents a complex and highly variable clinical syndrome that includes a broad range of disease severity and manifestations [1, 2]. Although conventional treatment strategies are routinely applied, a notable proportion of patients do not achieve adequate clinical improvement, indicating the need for adjunctive or alternative therapeutic options. This variability in response is largely attributable to the marked heterogeneity of sepsis, in which different biological endotypes and clinical phenotypes demonstrate diverse reactions to supportive and rescue therapies. Because of this heterogeneity, certain patients may require therapies beyond standard management. Identifying these non-responding subgroups is therefore essential for the development of targeted interventions. Over the years, numerous efforts have been made to classify sepsis into distinct subtypes based on clinical presentation, biomarker profiles, and underlying pathophysiological mechanisms [3]. Such classification systems aim to improve understanding of disease processes and to guide more effective, individualized treatment strategies. One commonly proposed approach stratifies sepsis according to the predominant dysregulated host immune response. Using this framework, patients may present with a hyperinflammatory phenotype, an immunosuppressive phenotype, or a mixed immune response. Each of these phenotypes is associated with different clinical trajectories and may require distinct therapeutic approaches to improve outcomes. Consequently, personalized strategies for managing septic shock may involve immunomodulatory therapies, extracorporeal support techniques such as hemoadsorption or extracorporeal membrane oxygenation (ECMO), and targeted interventions aimed at specific cellular or molecular pathways involved in sepsis pathogenesis [4]. Therefore, patients with a

low risk for adverse outcomes are candidates to receive conventional treatments. In contrast, patients with a high risk of clinical deterioration could benefit from specific therapies addressing their particular pathophysiological characteristics. This gives rise to so-called 'precision medicine' Figure 1 [4].

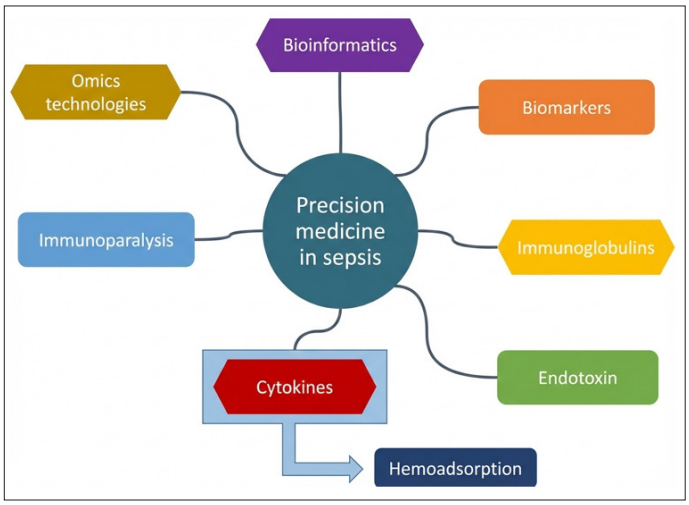

Figure 1: Precision medicine in sepsis integrates multiple biological and clinical domains to tailor treatment to an individual patient's immune and inflammatory profile. At the core is the idea that sepsis is not a uniform condition, but a dynamic and highly variable response to infection. Omics technologies (such as genomics, proteomics, and metabolomics) and bioinformatics help analyze large-scale biological data to identify patient-specific patterns and risk profiles. These insights support the identification of biomarkers that can indicate disease severity, immune status, or likely treatment response. Key immune-related factors include cytokines, which drive inflammation, endotoxin, which can trigger severe immune activation, and immunoglobulins, which reflect and support immune defense. The concept of immunoparalysis highlights how some patients shift from hyperinflammation to immune suppression, requiring different therapeutic strategies. Finally, interventions like hemoadsorption are shown as targeted treatments aimed at removing excessive inflammatory mediators, demonstrating how personalized data can guide more precise and effective sepsis management.

Clinical applicability of precision medicine describes the different endotypes with their specific potential treatments (e.g., immunoglobulins, endotoxin- and cytokine-hemadsorption, restoration of immunoparalysis) Table 1 [4].

Table 1: Clinical Applicability of Precision Medicine Strategies

Precision medicine strategy	Target (s)	Clinical application
Genomics and epigenomics	Genetic variants	Prognosis, severity
	Genotypes	Susceptibility to sepsis
Transcriptomics	Gene expression profiles, activity and regulation	Susceptibility to sepsis
	Sepsis response signatures	Severity, prognosis
Metabolomics	Small molecules produced by cells	Prognosis
	Metabolomic profile	Response to treatment
Proteomics	Proteins expressed by the genome under certain conditions	Diagnosis, Prognosis
	Biomarkers	Diagnosis, prognosis
Bioinformatics	Machine learning techniques	Diagnosis
		Prediction of clinical trajectories
		Assessment and treatment of organ dysfunction
		Clinical phenotypes
Biomarkers	Levels of molecules (mostly inflammatory)	Phenotypes
		Prediction of organ dysfuntion
		Allocation of hospital resources
		Diagnosis
		Severity
Immunoglobulins	Immunoglobulin levels	Detection and treatment of sepsis-associated hypogammaglobulinemia
Endotoxin and Hemoadsoption	Endotoxin levels and elimination by Hemoadsoption	Rescue therapy

Cytokines and Hemoadsoption	Cytokine levels and elimination by Hemoadsoption	Rescue therapy
Immunoparalysis	mHLA-DR expression	Immunoparalysis detection
		Immunoadjuvant treatment
		Stratification of patients
		GM-CSF therapy

In recent years, precision medicine has emerged as an increasingly important concept in both the identification of sepsis phenotypes and the selection of appropriate therapies. The primary goal of precision medicine is to tailor treatment to the individual patient by integrating clinical characteristics with biological and mechanistic insights [4]. In the existing literature, several terms are commonly used to describe severe or treatment-resistant septic shock, including "refractory septic shock," "catecholamine resistance," and "high-dose norepinephrine requirement." However, it is important to recognize that no universally accepted definitions currently exist for these conditions [5]. Differentiating patients with severe septic shock based on identifiable and potentially treatable traits may ultimately contribute to improved outcomes in this high-risk population.

Targeting Hyperinflammatory Phenotypes in Sepsis Management

Among the various sepsis phenotypes, the hyperinflammatory profile is characterized by an excessive and dysregulated immune response, which plays a major role in the development of organ dysfunction and poor clinical outcomes. This phenotype is driven by the overactivation of inflammatory pathways, leading to widespread endothelial injury, microcirculatory impairment, and metabolic derangements. Patients exhibiting this pattern often experience rapid clinical deterioration and may not respond adequately to standard therapeutic measures, thereby representing a subgroup that could benefit from phenotype-specific rescue interventions. Hyperinflammatory sepsis can be further subdivided according to the dominant inflammatory driver, most notably endotoxemia or excessive cytokine release. These subtypes differ in their underlying mechanisms and may require distinct therapeutic strategies to restore immune homeostasis and limit tissue damage.

High Endotoxin Hyperinflammatory Phenotype in Sepsis

Endotoxin, a structural component of the outer membrane of Gram-negative bacteria, has long been recognized as a key mediator in the pathogenesis of sepsis and septic shock. Elevated circulating endotoxin levels are strongly associated with disease severity, multiorgan dysfunction, and mortality [6, 7]. This recognition has led to the development of blood purification techniques aimed at removing endotoxin from the circulation, particularly through hemoadsorption-based therapies.

The largest randomized controlled trial evaluating endotoxin removal is the EUPHRATES trial, which enrolled 450 critically ill patients with septic shock and an endotoxin activity assay (EAA) value of at least 0.6 [8]. In this study, patients assigned to the intervention arm received two sessions of polymyxin B hemoperfusion, each lasting 90 to 120 minutes, in addition to standard care, while the control group received standard therapy with simulated hemoperfusion. The primary analysis demonstrated no significant difference in 28-day mortality between the two groups.

However, subsequent post hoc analyses provided important insights into patient selection. A subgroup analysis by Klein et al. focusing on patients with EAA values between 0.6 and 0.89 revealed a survival benefit among those treated with polymyxin B hemoperfusion compared with controls [9]. These findings suggest that extreme endotoxin burdens may limit the effectiveness of endotoxin removal, whereas patients with moderately elevated endotoxin levels may derive greater benefit. Supporting this hypothesis, recent observational and real-world studies have indicated improved survival and earlier recovery of organ dysfunction in selected endotoxemic septic shock patients treated with polymyxin B hemoperfusion [10, 11].

Further efforts to refine patient selection criteria have highlighted the importance of associated clinical features. A post hoc analysis combining data from the JSEPTIC-DIC study and the EUPHRATES trial demonstrated that septic patients with high endotoxin activity, abnormal coagulation parameters (international normalized ratio >1.4), and hyperlactatemia were more likely to benefit from polymyxin B hemoperfusion [12]. Additionally, subsequent investigations have emphasized that baseline organ failure severity, as assessed by SOFA scores, significantly influences treatment response [13]. Excessively high endotoxin loads may overwhelm adsorption capacity, thereby limiting therapeutic efficacy [14].

Currently, the TIGRIS trial is a prospective, multicenter, randomized study evaluating standard medical therapy with or without polymyxin B hemoadsorption in patients with septic shock, severe multiorgan dysfunction (MODS score >9), and EAA values between 0.60 and 0.89. Based on available evidence, patients with septic shock, significant organ dysfunction, hyperlactatemia, coagulation abnormalities, adequate source control, and moderately elevated endotoxin levels appear to be the most suitable candidates for endotoxin-targeted hemoadsorption therapy.

High Cytokine Hyperinflammatory Phenotype in Sepsis

In a subset of patients with septic shock and multiple organ dysfunction who fail to respond to conventional therapy, excessive cytokine release represents a dominant pathophysiological mechanism. This condition, often described as hypercytokinemia or cytokine storm, is characterized by markedly elevated circulating levels of proinflammatory mediators and is associated with hemodynamic instability, tissue injury, and high mortality. In such cases, hemoadsorption-based blood purification techniques have been proposed as individualized rescue therapies.

Hemoadsorption has been shown to effectively reduce circulating cytokine concentrations during systemic inflammation in humans, thereby attenuating the magnitude of the inflammatory response [15]. Other adsorption devices, such as HA330, have also demonstrated promising clinical and laboratory effects in patients with septic shock [16]. In addition, therapeutic plasma exchange has been explored as an alternative strategy to remove inflammatory mediators; however, its role remains under investigation and requires further validation [17].

Based on current evidence, cytokine hemoadsorption may be beneficial in a carefully selected subgroup of patients with severe septic shock, persistent hyperlactatemia, multiorgan failure, and extremely elevated cytokine levels [4]. Following the publication of best-practice recommendations, hemoadsorptive therapy should be considered in patients with septic or vasoplegic shock who exhibit markedly increased soluble inflammatory markers and show no improvement with standard treatment. Initiation of therapy is recommended within 12 hours of shock diagnosis and no later than 24 hours after onset [18]. Nevertheless, it is important to note that no universally accepted plasma cytokine threshold has been established to guide the initiation or discontinuation of therapy. Among the available inflammatory biomarkers, interleukin-6 (IL-6) has been the most frequently reported and studied cytokine in hemoadsorption research involving distributive shock. Several published studies have reported IL-6 plasma concentrations either as descriptive data or as inclusion criteria for patient enrollment (Table 2) [19-27].

Table 2: Studies that Have Reported Plasmatic Concentration of IL-6

IL-6 plasmatic concentration	Study summary or main findings
Treatment group: 23,300 (26,500) pg/ml.	7 patients
	Direct hemoperfusion (CYT-860, CYT-860-DHP)
	Different clinical criticall ill conditions with SOFA score of 12.93 (4.3).
Treatment group: [162–874] pg/ml	Randomized, controlled, open-label and multicentric.
Control group: 590 [125–2,147] pg/ml.	97 IMV patients who had severe sepsis or septic shock and ALI.
	Two groups: one receiving therapy with CytoSorb® hemoperfusion for 6 h per day for up to 7 consecutive days, and the other group receiving no hemoperfusion.
	Significant elimination of IL-6, ranging from 5% to 18% per blood pass throughout the entire treatment period. However, they did not observe any statistically significant differences in the secondary outcomes, such as the multiple organ dysfunction score, ventilation time, and time course of oxygenation.
Treatment group: 25,523 (1,052–491,260) pg/ml.	20 consecutive patients
	Refractory septic shock and CytoSorb® treatment was started after 7.8 (3.7) h of shock therapy.
	Noradrenaline dose could be significantly reduced after 6 (-0.4 μg/kg/min; p = 0.03) and 12 h (-0.6 μg/kg/min; p = 0.001).
Treatment group: 5,000 (939–5,000) pg/ml.	HA in septic shock with sepsis-associated AKI clinical picture.
Control group: not measured	76 patients
	They observed in patients treated with HA a shorter LOS and shorter therapeutic support such as catecholamine dependency and duration of RRT. However, in multivariate analysis (logistic regression for mortality, competing risk for length of stay), they found no significant differences.
Treatment group: 1,962.04 (229.09) pg/ml.	Septic shock, 100 patients whom 40 patients survived.
	In the survivor group, a remarkable reduction of biomarkers levels; PCT (65%, P = 0.5859), CRP (27%, P = 0.659), serum lactate (27%, P = 0.0159) and bilirubin (43.11%; P = 0.0565) were observed from baseline after CytoSorb® therapy. The vasopressors dosage remarkably decreased though it was not statistically different; 34.15% (P = 0.0816) forE, 20.5 % for NE (P = 0.3099) and 51% (P = 0.0678) forVP. A significant reduction in inflammatory markers; ILIL 6 and ILIL 10; (87% and 92%, P < 0.0001) and in tumor necrosis factor (24%, P = 0.0003) was also seen.
Treatment group:: 23,897 (23,179) pg/ml	Prospectively patients fulfilled refractory septic shock, IL-6 ≥ 1,000 ng/l and a vasopressor dependency index ≥ 3, despite adequate volume resuscitation.
Control group: 26,543 (21,373) pg/ml.	96 matched patients (48 treated with cytokine adsorption, 48 treated without).
	Cytokine adsorption was provided for three consecutive 24-h sessions initiated within 24 h from shock onset. Within the 72-h intervention period, circulating IL-6 levels (p = 0.254) and vasopressor requirements (p = 0.555) decreased irrespective of cytokine adsorption use. Intensive care mortality was more pronounced in patients treated with cytokine adsorption than in the control group (control: 20 (42%), cytokine adsorption: 32 (67%), p = 0.024) as evidenced by a competing risks hazard ratio for mortality of 1.82 (95% confidence interval, 1.03–3.2; p = 0.038).
Cytosorb® treatment: 60,529 (10,108–84,000,000) pg/ml. No-Cytosorb®: 25,660 (10,051–600,000) pg/ml.	Retrospectively patients with an IL-6 > 10,000 pg/ml.
	No difference in IL-6 reduction, hemodynamic stabilization, or mortality in patients with Cytosorb ® treatment compared to a matched patient population.

	However the underlying diseases resulting in hypercytokinemia were much varied, being separated as sepsis (different reasons except urosepsis) (21.0%), urosepsis (15.2%), septic shock (15.2%), ARDS (13.3%), hemorrhagic shock (8.6%), pneumonia (6.7%), polytrauma (4.8%), and others (15.2%).
Treatment group: 889.15 (1,307.43) pg/ml	Prospective, real time, investigator initiated, observational multicenter study, patients admitted to the ICU with sepsis and septic shock.
	45 patients were included and SOFA score was 12.90 (4.02).
	In the survivor group, the percentage dose reduction in vasopressor was norepinephrine (51.4%), epinephrine (69.4%) and vasopressin (13.9%) and a reduction in IL-6 levels (52.3%) was observed in the survivor group.
4,240 (0->107) pg/ml.	Cytosorb® registry, 1,434 patients.
	Indications for HA were sepsis/septic shock (n = 936); cardiac surgery perioperatively (n = 172); cardiac surgery postoperatively (n = 67) and "other" reasons (n = 259).
	At the end of HA, 80.6% of patients were alive. However, there was no significant difference in the predicted and actual hospital mortality. Just as in the whole cohort both the cardiovascular and the pulmonary subscores improved significantly and changes could be determined for CRP in 67.5%, PCT in 45.5% and IL-6 in 20.0% of patients.

Although many of these investigations have demonstrated effective cytokine removal and reductions in vasopressor requirements, consistent improvements in mortality or long-term outcomes have not been uniformly observed. These discrepancies likely reflect differences in patient selection, timing of intervention, underlying disease processes, and severity of immune dysregulation. The most severe end of the hypercytokinemia spectrum is represented by extremely elevated cytokine levels occurring early in the course of sepsis, often before clinical recognition. This condition is associated with refractory septic shock, rapid progression to multiorgan failure, and exceptionally high mortality. In this setting, nonselective blood purification techniques may provide a rapid reduction in inflammatory burden by broadly attenuating the cytokine storm, potentially improving short-term survival [28].

Targeted Sequential Hemoadsorption in Sepsis Management

Both endotoxemia and the excessive release of inflammatory mediators play a critical role in determining the severity and prognosis of sepsis and septic shock. Endotoxins act as potent triggers of the host inflammatory response, while the subsequent cytokine storm amplifies immune dysregulation and contributes to organ failure [7]. Sequential hemoadsorption has been proposed as a strategy to address both of these pathogenic drivers by combining endotoxin and cytokine removal in a stepwise manner. The primary objective of sequential hemoadsorption is to restore immune homeostasis by first eliminating the initiating inflammatory stimulus and then reducing the downstream overproduction of cytokines. Experimental and clinical data suggest that hemoadsorption can contribute to the rebalancing of immune responses in selected patients; however, endotoxin-targeted adsorption alone may be insufficient in cases where profound hypercytokinemia persists [29]. For this reason, a combined approach using polymyxin B–based endotoxin adsorption (PMX, Toraymyxin®) followed by cytokine adsorption with CytoSorb® has been applied in highly selected clinical scenarios [30]. Advances in precision medicine have facilitated improved identification of patients who may benefit from sequential hemoadsorption based on their phenotypic profile. Potential candidates include patients with refractory septic shock, severe multiorgan dysfunction, marked hypercytokinemia-particularly extremely elevated IL-6 concentrations-and significant endotoxemia. The rationale for this approach is to remove the primary inflammatory trigger responsible for sustaining immune dysregulation while simultaneously attenuating the secondary cytokine-driven inflammatory cascade.

Real-time monitoring of inflammatory biomarkers, especially plasma concentrations of IL-6 and IL-10, may assist clinicians in determining the optimal duration of therapy and the appropriate timing for discontinuation of hemoadsorption [31]. Although preliminary data are encouraging, the use of sequential hemoadsorption remains limited to selected patients, and further studies are needed to better define its role, timing, and impact on clinically meaningful outcomes.

Pathophysiology and Management of the Hypoinflammatory Sepsis Phenotype

In contrast to hyperinflammatory responses, a subset of patients with sepsis develops a hypoinflammatory or immunosuppressed phenotype, characterized by impaired immune function and reduced capacity to effectively clear infection. This state is marked by alterations in both innate and adaptive immune responses and is associated with increased susceptibility to secondary infections, prolonged intensive care stays, and higher late mortality. Recognition of this phenotype is essential, as immunosuppressive mechanisms may dominate the clinical course and require therapeutic approaches fundamentally different from those used in hyperinflammatory states. Patients with hypoinflammatory sepsis often exhibit diminished immune cell activity, altered antigen presentation, and decreased production of protective immunoglobulins. Among the most clinically relevant manifestations of this phenotype is hypogammaglobulinemia, which has emerged as a potential marker for identifying patients who may benefit from immune-supportive therapies.

Immunoglobulin Deficiency and Replacement Strategies in Septic Patients

Immunoglobulins play a central role in adaptive immunity by facilitating pathogen recognition, neutralization, and clearance [32]. In the context of sepsis, reduced levels of circulating immunoglobulins commonly referred to as hypogammaglobulinemia have been associated with worse clinical outcomes and increased mortality [33]. This observation has prompted interest in the use of immunoglobulin replacement therapy as a targeted intervention for selected patients. Although no universally accepted definition exists, hypogammaglobulinemia is frequently described as an IgG concentration below 500 mg/dL in patients older than five years or values falling more than two standard deviations below age-adjusted reference ranges [34]. Previous studies have demonstrated that particularly low levels of IgG1, IgM, and IgA are associated with reduced survival in

septic patients, underscoring the importance of both antibody quantity and subclass distribution. The administration of polyvalent intravenous immunoglobulins (IVIG) has been proposed as a rational approach to modulate the immune response in sepsis by simultaneously attenuating excessive inflammation and supporting antimicrobial defense mechanisms [35]. Clinical evidence suggests that preparations enriched with IgM and IgA may be especially beneficial. A meta-analysis including 19 randomized trials and more than 1,500 patients demonstrated a significant reduction in mortality among adults with sepsis treated with IgM- and IgA-enriched IVIG compared with albumin or no treatment [36]. The clinical syndrome of sepsis is initiated by the activation of multiple signaling pathways following the recognition of pathogen-derived molecules [pathogen-associated molecular patterns (PAMPs) e.g. endo- and exotoxins, DNA, lipids] and endogenous host-derived danger signals (damage-associated molecular patterns [DAMPs]) by specific cell-surface receptors on macrophages [toll-like receptors (TLRs)] [4]. Consequently, this leads to the expression of genes involved in inflammation, adaptive immunity, and cellular metabolism. During the course of sepsis, patients often present with multiple features of immunological alterations including systemic inflammatory responses, complement consumption, defects in neutrophil-mediated immunity and decreased serum levels of immunoglobulins finally causing immunosuppression Figure 2 [36].

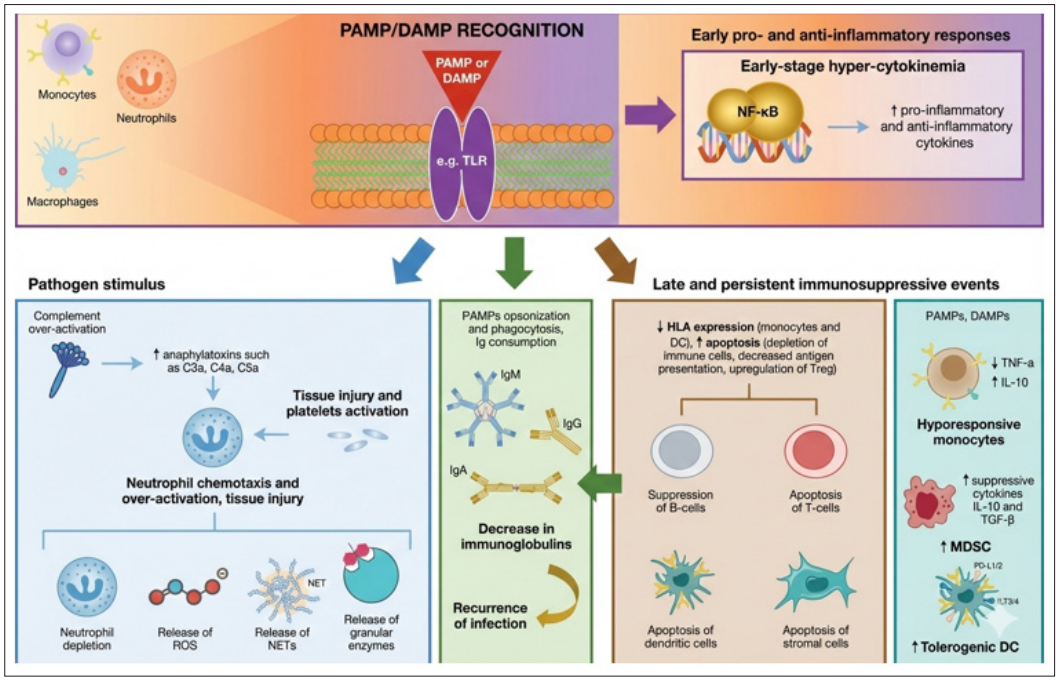

Figure 2: Immune response to pathogens or tissue damage as a dynamic process that begins with recognition of danger signals and can progress from inflammation to immunosuppression. When pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) are detected by pattern-recognition receptors such as Toll-like receptors (TLRs) on innate immune cells like monocytes, neutrophils, and macrophages, intracellular pathways activate transcription factors such as NF-κB. This leads to an early surge of both pro-inflammatory and anti-inflammatory cytokines, sometimes referred to as early-stage hyper-cytokinemia. At the same time, complement pathways may become overactivated, generating anaphylatoxins (C3a, C4a, C5a) that drive neutrophil chemotaxis, platelet activation, and tissue injury. Neutrophils can release reactive oxygen species (ROS), neutrophil extracellular traps (NETs), and granular enzymes, which help control infection but also contribute to collateral tissue damage and eventual neutrophil depletion. Meanwhile, antibodies such as IgM, IgG, and IgA bind to pathogens to promote opsonization and phagocytosis, but ongoing consumption of these immunoglobulins can reduce their levels and increase the risk of recurrent infection. In the later phase, the immune system may shift toward a prolonged immunosuppressive state characterized by reduced antigen presentation (lower HLA expression), increased apoptosis of immune cells such as T cells, B cells, and dendritic cells, and expansion of regulatory and suppressive cell populations. Monocytes become hyporesponsive, producing less pro-inflammatory cytokines like TNF-α and more suppressive mediators such as IL-10 and TGF-β, along with increased myeloid-derived suppressor cells and tolerogenic dendritic cells. This transition explains how an initially strong inflammatory response can evolve into immune paralysis, leaving the host vulnerable to secondary or persistent infections.

There have been several observations of decreased immunoglobulins among patients at sepsis diagnosis, in particular decreased levels of the three major immunoglobulin isotypes, immunoglobulins G, M and A (IgG, IgM and IgA, respectively) Table 3 [36].

Table 3: Studies Reporting on Immunoglobulin Levels and Kinetics in Patients with Sepsis

Study objective	Study design/enrolled patients	Immunoglobulin findings	Outcomes
Evaluate the time course of gamma-globulin concentrations in patients with septic shock, to define the frequency of low immunoglobulin concentrations, and to investigate the relationship of immunoglobulin concentrations to disease severity and outcome	Prospective observational study	76% of patients (16/21) had hypo-gammaglobulinemia (single or combined immunoglobulin deficiency) at admission: 7 patients had isolated low IgG concentrations, 4 patients had isolated low IgM concentrations, and 3 patients had low IgG and IgM concentrations	Patients with low IgG concentrations were indistinguishable at baseline from patients with normal IgG concentrations but had fewer vasopressor-free days (P=0.02) and more frequently developed acute lung injury/acute respiratory distress syndrome (P=0.02)
	21 patients (aged≥18 years old) with community-acquired septic shock	Two patients had low concentrations of IgG, IgM, and IgA and died	There was no significant difference in outcomes in patients with normal or low IgM levels
		with refractory shock within 2 days	All deaths occurred in patients with low IgG concentrations (P=0.01)
		Patients with low IgG concentration on Day 1 had persistent low levels throughout the ICU stay. Almost all patients with normal IgG levels maintained normal concentrations throughout their stay (1 patient had a transient decrease in IgG on Day 3)	
Investigate the time course of IgG and IgM concentrations in patients who developed septic shock during their ICU stay	Observational cohort study	45% of patients (17/38) had hypo-gammaglobulinemia (single or combined immunoglobulin deficiency) on admission: 7 patients had isolated low IgG levels, 5 patients had isolated low IgM concentrations, and 5 patients had low IgG and IgM levels	There were no significant differences regarding length of ICU or hospital stay, oxygenation index (PaO2/FIO2), duration of vasopressor use, or duration of mechanical ventilation in those with low or normal IgG levels
	38 patients who developed septic shock during their ICU stay	Low levels of IgG were resolved within 10 days in the 5 patients who survived in the group with low IgG	No comparative analyses were provided for patients with low or normal IgM levels
		IgM concentrations improved over time in patients with and without low IgG levels	
Evaluate the quantitative changes in the status of immunocompetence in severe sepsis over time and its potential influence on clinical outcome	Prospective observational cohort study	Survivors exhibited a progressive increase in IgG, IgA, and IgM levels from Day 1 to Day 10	Compared to survivors, septic patients who did not survive had significantly lower levels of IgG in the first 24 h following admission to the ICU
	50 patients (aged≥18 years old) with severe sepsis or septic shock		There was no significant difference in IgA or IgM levels between survivors and non-survivors
Measure the endogenous levels of circulating IgG, IgA, and IgM in a cohort of septic shock patients	Prospective observational cohort study	At Days 1–2, 61%, 40%, and 9% of patients had IgG, IgM, and IgA concentrations below the lowest limit of age-matched reference values, respectively	Changes in immunoglobulin levels did not appear to be associated with increased mortality, morbidity, or severity after septic shock
62 consecutive patients (aged≥18 years old) with septic shock	62 consecutive patients (aged≥18 years old) with septic shock	Circulating IgG and IgM concentrations increased over time, by Days 5–7, 61% of patients had IgG and IgM levels within the range of normal values	Reduced immunoglobulin level was correlated with reduced protein concentrations at Days 1–4 suggesting an apparent hypogammaglobulinemia is present during this time period in septic shock patients

Investigate the relationship between endogenously produced immunoglobulins and the clinical outcome in septic shock	Retrospective study	Both patients with systemic inflammatory response syndrome and septic shock showed subnormal levels of total IgG, IgG2, and IgM	Patients with septic shock who died showed the lowest levels of total IgG and IgG1
Investigate the relationship between endogenously produced immunoglobulins and the clinical outcome in septic shock	42 patients with septic shock and 36 patients with systemic inflammatory response syndrome		Univariate Cox regression analysis showed that levels of IgG1, IgG2, IgG3, IgM, IgA, and total IgG were inversely associated to the probability of death at 28 days
			Multivariate analysis showed that IgG1, total IgG, IgM, and IgA behaved as independent protective factors against mortality (HR, P): 0.23, 0.026; 0.16, 0.028; 0.11, 0.042; 0.05, 0.010, respectively
Investigate the kinetics of IgM during the different stages of sepsis	Prospective observational multicenter cohort study	Serum IgM was decreased in septic shock compared to patients with systemic inflammatory response syndrome and patients with severe sepsis	Serial measurements in patients who progressed from severe sepsis to septic shock, beginning from the early start of vasopressors, showed that the distribution of IgM over time was significantly greater for survivors than for non-survivors
	332 critically ill patients were enrolled	Paired comparisons at distinct time points of the sepsis course showed that IgM was decreased only when patients deteriorated from severe sepsis to septic shock	
Assess the frequency of hypogammaglobulinemia in patients with systemic inflammatory response syndrome, severe sepsis, and septic shock	Retrospective study 708 patients with systemic inflammatory response syndrome, severe sepsis, and septic shock	IgG, IgA, and IgM hypogammaglobulinemia was demonstrated in 25%, 3%, and 12% of patients with severe sepsis, and 24%, 2%, and 13% of septic shock patients, respectively	Mortality in patients with severe sepsis or septic shock and IgG hypogammaglobulinemia was significantly higher than in those with normal IgG levels
Evaluate the association between immunoglobulin levels in plasma and survival in patients with severe sepsis	Prospective observational multicenter cohort study	At time of diagnosis, 27.9%, 39.2%, and 19.2% of patients had immunoglobulin concentrations below the normal reference values for IgG1, IgM, and IgA, respectively	Kaplan–Meier analysis showed that levels below normal reference values for IgG1, IgM, and IgA were associated with shorter survival times
	172 patients (aged > 18 years old) admitted to the ICU with severe sepsis/septic shock		Multivariate regression analysis showed that low levels of IgG1 were a risk factor for mortality (OR: 2.50, 95% CI 1.04–6.03; P = 0.042)
			The combined presence of IgG1, IgM, and IgA levels below the normal threshold had a synergistic impact on mortality risk (OR: 5.27, 95% CI 1.41–19.69; P = 0.013). A similar effect was observed for combined low levels of IgG1 and IgA:,and IgG1 and IgM
Evaluate the additional mortality risk associated with subnormal IgG concentrations in adults with sepsis managed in an ICU setting	Systematic review of 8 studies	IgG concentrations increased over time in most studies	Subnormal IgG levels on the day of sepsis diagnosis did not increase the risk of death in adult patients with severe sepsis and/or septic shock by both fixed effect and random effect meta-analysis (M-H pooled OR: 1.32 [95% CI 0.93–1.87] and D + L pooled OR: 1.48 [95% CI 0.78–2.81], respectively)
	438 adult patients with sepsis		
Study the relationship between circulating B cells and plasma IgM levels and sepsis survival rate	Systematic review and meta-analysis of 11 studies	Plasma IgM level was significantly decreased in septic patients (SMD = −2.35, 95% CI −2.94, −1.76; P < 0.00001, I2 = 0%) compared with healthy controls	The reduction of circulating B cells and IgM plasma levels is negatively correlated with sepsi

	829 patients (aged > 18 years old) with sepsis and/or septic shock	Plasma IgM level was significantly lower in sepsis survivors versus sepsis non-survivors (SMD = −0.31, 95% CI −0.53, −0.09; P = 0.005, I2 = 50%)	

Despite these encouraging findings, uncertainty remains regarding optimal dosing strategies, timing of administration, and patient selection criteria. Current recommendations vary and include administering a single dose of polyclonal IgG at 1–2 g/kg body weight (level of evidence 2C) [37], or alternative regimens involving IgM- and IgA-enriched IVIG given at 250 mg/kg/day over a 10-hour infusion for three consecutive days [38], or 42 mg/kg daily for five days [39]. It is important to note that the 2021 Surviving Sepsis Campaign guidelines do not recommend routine IVIG administration for all septic patients, particularly those with normal immunoglobulin levels. However, patients with documented hypogammaglobulinemia may represent a subgroup more likely to benefit from immunoglobulin therapy. Further high-quality studies are needed to better define this population and establish clear treatment protocols [39].

Balancing Immune Dysregulation in Sepsis Through Precision Immunotherapy

Sepsis is a complex and dynamic syndrome in which patients may exhibit varying degrees of immune dysregulation over time. At the extremes of this dysregulation are two opposing yet equally harmful states: excessive inflammation, commonly referred to as a cytokine storm, and profound immunosuppression, often described as immune paralysis. Both conditions are associated with unfavorable short- and long-term outcomes, and their coexistence or sequential appearance within the same patient further complicates management. Hyperinflammatory responses are characterized by uncontrolled immune activation, leading to widespread tissue injury, endothelial damage, and progressive organ dysfunction. In contrast, immune paralysis reflects an exhausted immune system that is unable to mount an effective response against ongoing or secondary infections, thereby increasing the risk of nosocomial infections, prolonged hospitalization, and late mortality. The primary challenge in developing effective immunomodulatory therapies lies in accurately identifying the dominant immune phenotype and selecting the appropriate intervention at the right time. Given the substantial heterogeneity of sepsis, uniform treatment strategies are unlikely to be effective for all patients. During the early phase of sepsis, patients exhibiting a hyperinflammatory profile are at particularly high risk of mortality within the first ten days of illness. This state is often driven by excessive production of interleukin-1β (IL-1β) by activated tissue macrophages, which contributes to disseminated intravascular coagulation, liver dysfunction, bone marrow hemophagocytosis, and pancytopenia. Collectively, these manifestations are described as macrophage activation syndrome (MAS) [40]. Using tools such as the HScore [41] and the criteria proposed by Shakoory and colleagues [42], macrophage activation-like syndrome (MALS) has been estimated to occur in approximately 3.7% to 4.3% of patients with sepsis. Ferritin has emerged as a key biomarker for identifying this phenotype. Ferritin levels exceeding 4,420 ng/mL demonstrate high specificity (98.0%) and a strong negative predictive value (97.2%) for the diagnosis of MALS [43]. Post hoc analyses of randomized controlled trials have shown that treatment with anakinra, a recombinant IL-1 receptor antagonist, was associated with improved survival in septic patients exhibiting features of MALS [43]. At the opposite end of the immune spectrum are patients with immunoparalysis, whose immune systems are profoundly suppressed [44]. This condition is characterized by functional exhaustion of immune cells and is associated with increased vulnerability to secondary infections and poor outcomes. Reduced expression of human leukocyte antigen-DR (HLA-DR) on circulating monocytes has been proposed as a hallmark of immunoparalysis and a useful biomarker for patient identification [45]. Exploratory clinical studies suggest that this state may be reversible through targeted immune-stimulating therapies, including recombinant human interferon-γ (rhIFN-γ) [46], hematopoietic growth factors such as G-CSF and GM-CSF, thymosin alpha-1, recombinant human IL-7 (CYT107), and immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway [47-49].

However, immunostimulatory treatments are unlikely to benefit all septic patients and may even be harmful if applied indiscriminately. It is estimated that immunoparalysis occurs in only 25%–30% of patients with sepsis, underscoring the importance of careful patient selection. The PROVIDE randomized controlled trial recently identified three distinct immune response patterns in sepsis MALS, immunoparalysis, and an intermediate phenotype—supporting the use of biomarker-guided stratification for personalized immunotherapy [50]. In this double-blind trial, patients were classified based on serum ferritin levels and HLA-DR expression and randomly assigned to receive anakinra, rhIFN-γ, or placebo. Patients in the immunotherapy arm demonstrated improved early survival and reductions in organ dysfunction compared with placebo, highlighting the potential of precision immunotherapy in selected subgroups. Interleukin-1β occupies a central role at the interface between innate and adaptive immunity. Produced by myeloid cells in response to pathogen-associated and damage-associated molecular patterns, IL-1β promotes downstream inflammatory signaling, including the induction of IL-6 production [51, 52]. Recent advances have identified novel low-molecular-weight IL-1β antagonists that block receptor binding, opening new avenues for targeted immunotherapy in sepsis [53]. Tumor necrosis factor-α (TNF-α) has also been extensively studied as a therapeutic target. A meta-analysis of 17 studies involving nearly 9,000 patients demonstrated a modest but significant reduction in 28-day mortality with anti-TNF-α therapy compared with placebo, particularly in patients with high IL-6 levels or septic shock [54]. Additional immune-regulatory pathways, including immune checkpoint inhibition of PD-1 and PD-L1, have shown promise in restoring immune function. Early clinical studies using nivolumab, a PD-1 inhibitor, have demonstrated acceptable safety and tolerability in septic patients [55-57].

Vasoplegia and Catecholamine Resistant Hypotension in Septic Shock

Profound systemic vasodilation and persistent arterial hypotension are defining features of septic shock. When adequate fluid resuscitation fails to restore mean arterial pressure and tissue perfusion, vasopressor therapy becomes necessary. Norepinephrine, a potent α-adrenergic agonist, is currently recommended as the first-line vasopressor for septic shock–associated hypotension. However, increasing exposure to adrenergic agents has been associated with adverse effects, including arrhythmias, metabolic disturbances, organ dysfunction, and increased mortality [58, 59]. A subset of patients develops catecholamine-resistant hypotension, a condition characterized by diminished vascular responsiveness

to adrenergic vasopressors despite escalating doses. This clinical phenotype reflects severe vasoplegia and altered vascular signaling pathways and is associated with poor prognosis. In such cases, non-adrenergic vasopressors and adjunctive therapies may provide benefit by targeting alternative mechanisms of vascular tone regulation.

Non Adrenergic Vasopressors: Therapeutic Roles of Vasopressin and Angiotensin II

The renin angiotensin aldosterone system (RAAS) represents a fundamental physiological mechanism for maintaining arterial blood pressure under conditions of hypovolemia and circulatory stress, such as septic shock [60]. Beyond its hemodynamic role, angiotensin-II (AT-II) influences inflammation, apoptosis, coagulation, cellular metabolism, and mitochondrial function, all of which are relevant to sepsis pathophysiology [61,62]. The timing and sequencing of vasopressor therapy in distributive shock have gained increasing attention, particularly with respect to early multimodal approaches. While norepinephrine remains the cornerstone of treatment, the initiation of second- or third-line vasopressors has been widely debated. Vasopressin is the most extensively studied adjunctive agent and is currently suggested by the Surviving Sepsis Campaign for patients with septic shock who remain hypotensive despite low-to-moderate doses of norepinephrine, although this recommendation is classified as weak due to moderate-quality evidence [63]. Evidence supporting vasopressin use largely originates from subgroup analyses of randomized trials and observational studies. These data suggest that vasopressin may confer greater benefit when initiated in less severe shock or at lower norepinephrine doses. In the VASST trial, patients receiving less than 15 μg/min of norepinephrine demonstrated improved survival when vasopressin was added compared with norepinephrine alone [64]. A proposed mechanism underlying this benefit is the reduction of cumulative catecholamine exposure, thereby limiting adrenergic-related toxicity [65]. Angiotensin-II is an endogenous hormone with vasoconstrictive effects at both arterial and venous levels and has been approved by the U.S. Food and Drug Administration for the treatment of distributive shock [66]. Initial safety and efficacy data from a pilot study by Chawla et al. demonstrated that AT-II effectively increased blood pressure in patients with catecholamine-resistant hypotension without an increase in serious adverse events [67]. Rates of tachyarrhythmias, ischemic complications, and cardiac arrhythmias were comparable between treatment and placebo groups. The ATHOS-3 randomized controlled trial further evaluated AT-II in 344 patients with refractory vasodilatory shock receiving high-dose catecholamines. The primary endpoint an increase in mean arterial pressure of at least 10 mmHg or achievement of MAP ≥75 mmHg was reached in 69.9% of patients treated with AT-II compared with 23.4% in the placebo group, without significant differences in adverse effects [68]. Subsequent post hoc analyses revealed that initiating AT-II at lower norepinephrine-equivalent doses (≤0.25 μg/kg/min) was associated with improved survival [69]. Additional subgroup analyses from ATHOS-3 identified patient populations that may derive particular benefit from AT-II therapy. Patients requiring renal replacement therapy at baseline demonstrated higher rates of renal recovery and improved survival [70], while those with low angiotensin I/II ratios suggesting endogenous AT-II deficiency also showed improved outcomes [71]. More recently, elevated plasma renin concentrations have been proposed as a biomarker for identifying patients most likely to benefit from AT-II administration [72]. Taken together, these findings highlight significant heterogeneity within the RAAS response in vasodilatory shock. Although AT-II should not be considered a first-line vasopressor, current evidence supports its use as an adjunctive agent in selected patients with distributive shock, particularly those with renal failure, elevated renin levels, and persistent hypotension despite moderate catecholamine dosing [73].

Glucocorticoids in Sepsis

Septic shock results from uncontrolled widespread inflammation, which can lead to multi-organ failure and death. It is now recognized that an inadequate activation of the hypothalamic-pituitary-adrenal (HPA) axis in the host plays a major role in driving the severe systemic inflammatory response during infections. Proinflammatory mediators at sites of inflammation suppress the body's anti-inflammatory mechanisms, but this effect can be mitigated through the administration of exogenous corticosteroids. In sepsis, corticosteroids work via both genomic and nongenomic mechanisms to stabilize the cardiovascular system, reduce systemic and tissue inflammation, support organ recovery, and prevent mortality [74]. Current SSC guidelines suggest considering corticosteroid therapy in adult patients with septic shock who require ongoing vasopressor support, particularly when the catecholamine-equivalent dose exceeds 0.25 μg/kg/min for at least 6 hours. Recent randomized controlled trials (RCTs) and meta-analyses have further evaluated this approach. Annane et al. [75] assessed hydrocortisone combined with fludrocortisone, drotrecogin alfa-activated, and the combination of these treatments, finding that 90-day all-cause mortality was lower in patients receiving hydrocortisone plus fludrocortisone compared to placebo. Additionally, the hydrocortisone-fludrocortisone group had more vasopressor-free days up to day 28 (17 vs. 15 days, $P < 0.001$) and more organ-failure-free days (14 vs. 12 days, $P = 0.003$). Venkatesh et al. [76] randomized mechanically ventilated patients with septic shock to receive hydrocortisone at 200 mg per day or placebo for 7 days, or until death or ICU discharge. While hydrocortisone did not reduce 90-day mortality compared to placebo, it did lead to a faster resolution of shock and a shorter duration of the first episode of mechanical ventilation. An updated meta-analysis [77] confirmed that systemic corticosteroids accelerate shock resolution (mean difference 1.52 days; 95% CI 1.71–1.32). Finally, the RECORD trial [78] aims to identify patient subgroups that are more likely to respond to corticosteroid therapy. The study explores whether sepsis caused by community-acquired pneumonia, septic shock, sepsis-related ARDS, or bacterial and viral infections may share common responsiveness signatures.

Corticosteroids, Vitamin C, and Thiamine in Sepsis

In septic shock, tissue injury progresses rapidly, with mitochondrial dysfunction playing a key role. This mitochondrial impairment disrupts energy production and uncouples oxidative phosphorylation, leading to oxidative stress. Oxidative stress is characterized by elevated reactive oxygen species (ROS) and reactive nitrogen species (RNS), which damage cell membranes, intercellular junctions, and the endothelial barrier, ultimately harming the glycocalyx [79]. Additionally, it affects vascular tone, increases capillary permeability, and causes partial resistance to catecholamines [80]. Because of these intracellular effects, corticosteroids, ascorbic acid (vitamin C), and thiamine have been proposed as part of an adjunctive therapy for sepsis, known as "metabolic resuscitation."

The clinical relevance of high-dose vitamin C combined with hydrocortisone and thiamine, often referred to as the "sepsis cocktail," was highlighted by Marik et al. [81]. Their study showed significant reductions in hospital mortality, vasopressor

dependence, and organ dysfunction. A noteworthy meta-analysis [82] examined both corticosteroids and the metabolic resuscitation cocktail (hydrocortisone, vitamin C, and thiamine). Although mortality differences were not statistically significant, the combination improved organ dysfunction, measured by ΔSOFA over the first 72 hours, and reduced the need for vasoactive drugs.

However, a more recent study by Lamontagne et al [83]. reported harmful effects of vitamin C in sepsis, including increased morbidity and 28-day mortality. This analysis helped clarify lingering uncertainties regarding vitamin C use in septic patients. Still, a subgroup of patients with refractory septic shock-who have particularly high mortality rates-was underrepresented, with fewer than 60% of the study population meeting septic shock criteria. In this subgroup, outcomes from vitamin C therapy were inconclusive. Moreover, the combined therapy of hydrocortisone, vitamin C, and thiamine, which has the strongest physiological rationale, was not evaluated in this trial [84]. In patients with sepsis organ failure and death, it is usually a result of the host's response to the infecting pathogen rather than from the infecting pathogen itself. This was first recognized by Sir William Osler, who commented that "except on few occasions, the patient appears to die from the body's response to infection rather than from the infection". Sepsis is fundamentally an inflammatory disease mediated by the activation of the innate immune system by both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). Calvano et al. demonstrated that exposure of blood leukocytes to bacterial endotoxin (LPS) altered the expression of 3714 genes. These include genes for pro- and anti-inflammatory cytokines, chemokines, adhesion molecules, transcription factors, enzymes, clotting factors, stress proteins and anti-apoptotic molecules. These inflammatory mediators have widespread pathophysiologic consequences, including vasoplegic shock, myocardial dysfunction, altered microvascular flow and diffuse endothelial injury. However, fundamentally, sepsis is characterized by the excessive production of reactive oxygen species (ROS) by the induction of enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase (NOX) and the uncoupling of mitochondrial oxidative phosphorylation Figure 3 [84].

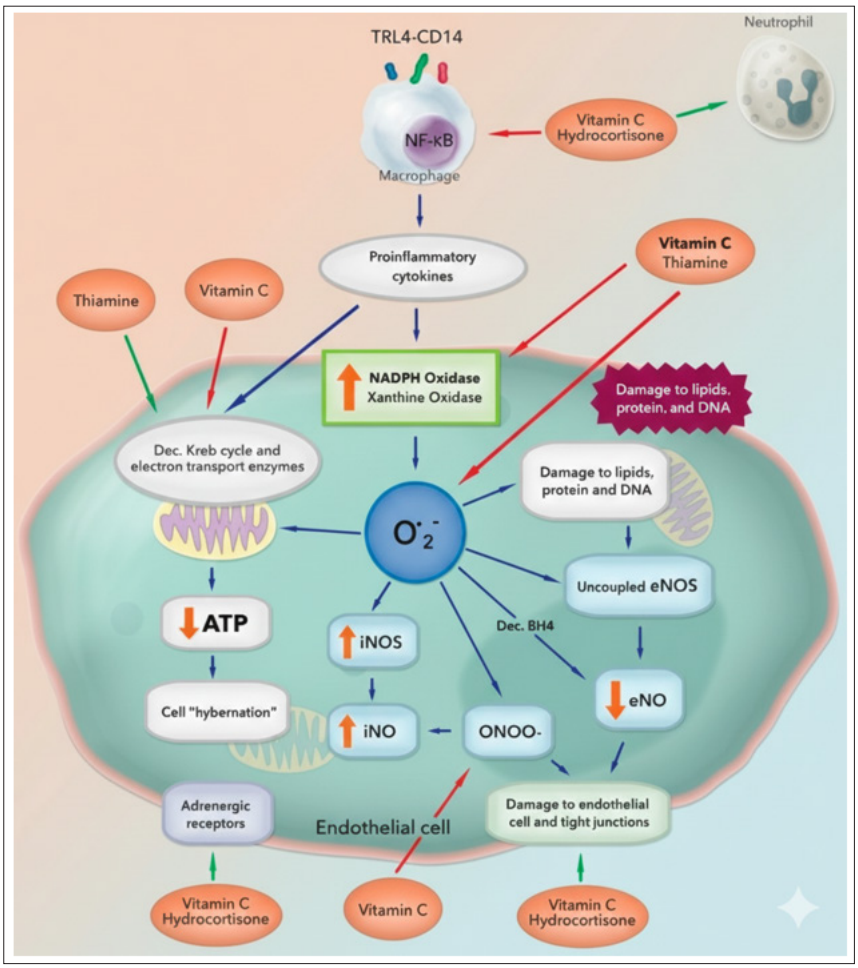

Figure 3. Inflammatory signaling and oxidative stress affect endothelial cell function during severe infection or systemic inflammation, and how vitamins and steroids may modulate these processes. Activation of macrophages through the TLR4-CD14 receptor complex triggers NF-κB signaling, leading to the release of proinflammatory cytokines that stimulate enzymes such as NADPH oxidase and xanthine oxidase in endothelial cells. These enzymes generate large amounts of superoxide and other reactive oxygen species (ROS), which damage lipids, proteins, and DNA and impair mitochondrial function by reducing Krebs cycle and electron transport chain activity, ultimately lowering ATP production and pushing the cell into a low-energy "hibernation" state. At the same time, inflammatory signaling increases inducible nitric oxide synthase (iNOS), raising nitric oxide (NO) levels that can react with superoxide to form peroxynitrite, a highly toxic oxidant that further injures cellular structures and depletes tetrahydrobiopterin (BH4), a cofactor needed for proper endothelial nitric oxide synthase (eNOS) function. When eNOS becomes uncoupled, it produces more superoxide instead of protective NO, worsening oxidative stress and leading to reduced NO bioavailability, endothelial dysfunction, and breakdown of

tight junctions. The diagram also highlights potential protective roles of vitamin C, thiamine, and hydrocortisone: vitamin C can scavenge ROS, support mitochondrial enzymes, preserve BH4, and help restore NO signaling; thiamine supports cellular energy metabolism by maintaining Krebs cycle activity; and hydrocortisone modulates inflammatory signaling and adrenergic receptor responsiveness. Together, these interventions are depicted as reducing oxidative damage, stabilizing the endothelium, and improving cellular energy balance during inflammatory stress.

Vitamin C suppresses activation of NF-κB by inhibiting tumor necrosis factor-α (TNFα) induced phosphorylation of inhibitory kappa-B kinase (IκB kinase). Ascorbic acid decreases high mobility group box 1(HMGB1) secretion; HMGB1 is an important late pro-inflammatory cytokine. Vitamin C may decrease the synthesis and inactivate histamine [58]; histamine has been shown to play an important role in sepsis. Vitamin C is an essential co-factor for the synthesis of norepinephrine, epinephrine and vasopressin; in addition vitamin C increases adrenergic transmission. Vitamin C may decrease the immunosuppression associated with sepsis. It has been known for over 60 years that vitamin C has immune-enhancing properties. It was initially assumed that vitamin C was directly viricidal (in vivo) and this mistaken belief underlies the recommendations of Linus Pauling who promoted the use of large doses of oral vitamin C (up to 18 g/day) for the prevention and treatment of the common cold. A number of RCTs have reported that vitamin C supplementation had no effect on the incidence of the common cold. However, vitamin C has been shown to decrease the incidence of the common cold if the person is under enhanced stress, e.g., cold temperatures and/or physical stress. While high dose vitamin C has in-vitro viricidal properties, there is no data or physiologic rationale to suggest that this occurs in vivo. Rather, the "anti-viral" effect of vitamin C are likely due to that fact that vitamin C has specific immune-enhancing effects. Vitamin C is concentrated in leucocytes, lymphocytes and macrophages, reaching high concentrations in these cells. Vitamin C improves chemotaxis, enhances neutrophil phagocytic capacity and oxidative killing, stimulates interferon production, and supports lymphocyte proliferation. The major presumed beneficial effects of vitamin C in patients with sepsis are outlined in Table 4 [84].

Table 4: Summary of Key Roles of Vitamin C in Sepsis

Key Role	Mechanism
Antioxidant	Scavenges extracellular, intracellular and mitochondrial ROS; limits oxidation of mitochondrial proteins, enzymes, lipoproteins, cell membrane, etc.
Anti-inflammatory	Inhibits activation of NFκB, decreases HMGB1, inhibits histamine, prevents NETosis, inactivates HIF-1α
Microcirculation	Increases eNOS, decreases iNOS, preserves tight junctions
Immune function	Supports lymphocyte proliferation, increases neutrophil bacteriocidal action, improves chemotaxis, stimulates interferon production, decreases T regulatory cells (Tregs)
Anti-thrombotic	Decreases platelet activation and tissue factor expression, increases thrombomodulin
Synthesis of catecholamines	Acts as a cofactor in synthesis of epinephrine, dopamine and vasopressin.Increases adrenergic sensitivity
Wound Healing	Hydroxylation of procollagen, increased expression of collagen mRNA

Thus far, the individual or partial combination use of these three metabolic resuscitation agents has not yielded the expected benefits. Future studies need to consider several factors: whether the vitamin C dose was adequate, whether its administration should be guided by plasma levels, what the optimal timing and duration of therapy might be, which biomarkers are relevant for its use, which outcomes should be measured, and which critically ill patients are most likely to benefit [85].

Veno Arterial ECMO for Septic Shock with Severe Cardiac Dysfunction

The concept of the "low flow phenotype" to describe patients with septic cardiomyopathy who continue to show evidence of inadequate tissue perfusion despite receiving vasoactive agents and supportive care tailored to other phenotypes. The role of mechanical circulatory support in the management of refractory septic shock in adults remains debated. Among the available options, veno-arterial (VA) ECMO is considered particularly attractive for patients with combined severe cardiac and pulmonary dysfunction, although robust evidence in adult populations is still lacking. Riera and colleagues [86] reviewed the literature and emphasized that ECMO should be regarded as a supportive strategy rather than a definitive treatment, yet they noted that in carefully selected cases, with appropriate configuration and management, it can be life-saving for septic patients with no other therapeutic alternatives. In a multicenter retrospective study, Bréchot et al. [87] found that patients treated with VA-ECMO had more profound myocardial impairment, hemodynamic instability, and organ failure compared with controls ($p < 0.0001$ for each), but nonetheless achieved significantly better 90-day survival (60% vs. 25%; risk ratio for mortality 0.54, 95% CI 0.40–0.70; $p < 0.0001$). Similarly, Ling et al. [88] performed a systematic review of 14 observational studies involving 468 patients, concluding that VA-ECMO can improve survival in septic shock when severe sepsis-induced myocardial depression is present. Outcomes, however, were poor in patients without marked left ventricular dysfunction. Overall pooled survival was 36.4% (95% CI 23.6–50.1%), with markedly better survival in those with left ventricular ejection fraction (LVEF) below 20% (62.0%, 95% CI 51.6–72.0%) compared with patients whose LVEF exceeded 35% (32.1%, 95% CI 8.69–60.7%; $p = 0.05$).

Pathophysiology and Therapeutic Targets in Sepsis Associated Endothelial Dysfunction

Sepsis exerts profound effects on endothelial cell (EC) function and plays a central role in the progression from sepsis to organ failure. Key endothelial processes disrupted during sepsis include vasoregulation, barrier integrity, inflammatory signaling, and hemostasis. These disturbances are often linked to glycocalyx degradation, which contributes to altered nitric oxide metabolism, increased production of reactive oxygen species due to weakened antioxidant defenses, impaired intercellular communication, protease activity, exposure of adhesion molecules, and activation of tissue factor, among other mechanisms [89].

Within the inflammatory cascade, bacterial components stimulate both immune cells and the endothelium, driving cytokine release in a self-sustaining cycle. Endothelial activation leads to the expression of adhesion molecules, enabling immune cell binding and subsequent transmigration to sites of injury. Reactive oxygen species generated by immune cells and ECs intensify the inflammatory response, resulting in glycocalyx loss, enhanced adhesion molecule expression, increased vascular permeability,

and endothelial apoptosis. Chemokines produced by immune and endothelial cells further recruit bone marrow–derived immune cells. A shift in the balance between endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) promotes excessive nitric oxide production, culminating in vasodilation [90].

When there is a breach allowing a pathogen to enter the blood stream, generalized inflammation from exposure to bacterial components and tissue breakdown products occurs. While immune cells ensure an adequate response to the insult, endothelium is also activated and is thought to direct and modulate the inflammatory response. During severe inflammation, such as seen in sepsis, the activation of an inflammatory cascade by the pathogen. NF-κB plays a crucial role in the cell (both inflammatory cells and ECs) response to cytokines or bacterial cell wall components [i.e. lipopolysaccharide (LPS)]. LPS forms a complex with LPS-binding protein, MD-2, toll-like receptor-4 (TLR-4), and CD14, further initiating intracellular signalling.9 The downstream pathways can be crudely divided in two competitive pathways: TLR4/TRIF/IRF3 and TLR4/MyD88/NF-κB. The TLR4/TRIF/IRF3 pathway involves activation of TRIF, internalization of the TLR4/TRIF complex within endosomes with subsequent activation of interferon regulatory transcription factor-3 (IRF3) and interferon production. At the same time, activation of the TLR4/MyD88/NF-κB pathway leads to phosphorylation of MyD88 and interleukin-1 receptor-associated kinases 1 and 4 (IRAK1 and IRAK4). IRAKs in turn phosphorylate TNF receptor-associated factor 6 (TRAF6), which promotes degradation of IκB and nuclear translocation of NF-κB. TRAF6 is also thought to activate mitogen-activated protein kinases (MAPKs), ultimately resulting in activation of activator protein-1 (AP-1). Inflammatory cytokines, such as TNF-α, can activate similar pathways resulting in nuclear translocation of NF-κB, further increasing cytokine production.10 Although immune cells are responsible for most cytokine production during sepsis, ECs are not only the target of cytokines, but are also, via similar pathways, able to secrete such cytokines as IL-1β, IL-6 and interferon. While the exact role of endothelial-derived cytokines is unclear, current thought is that ECs contribute to ramping up and modulating the inflammatory cascade and play an important role in activation and fine tuning of the local immune response Figure 4 [90].

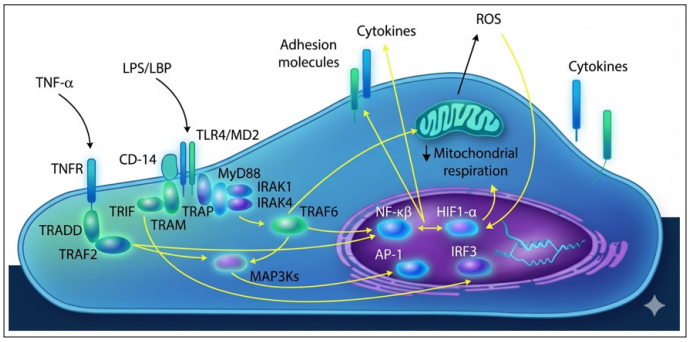

Figure 4: Bacterial components and inflammatory signals activate intracellular pathways that lead to cytokine production and metabolic changes in a cell, particularly through Toll-like receptor 4 (TLR4) and tumor necrosis factor (TNF) signaling. When lipopolysaccharide (LPS) bound to LPS-binding protein (LBP) engages CD14 and the TLR4-MD2 receptor complex on the cell surface, adaptor proteins such as MyD88, TRIF, TRAM, and TRAP are recruited. These adaptors activate downstream kinases including IRAK1, IRAK4, TRAF6, and MAP3Ks, which transmit signals into the nucleus. In parallel, TNF-α binds to the TNF receptor (TNFR), recruiting proteins like TRADD and TRAF2 that converge on similar signaling cascades. These pathways activate transcription factors such as NF-κB, AP-1, IRF3, and HIF-1α, which move into the nucleus and drive the expression of proinflammatory cytokines, adhesion molecules, and other immune response genes. At the same time, mitochondrial function is altered, with reduced mitochondrial respiration and increased production of reactive oxygen species (ROS), which can further amplify inflammatory signaling. The combined effect is enhanced cytokine release, increased cell adhesion and immune cell recruitment, and a feedback loop that sustains and intensifies the inflammatory response. Sepsis also initiates the coagulation cascade through activation of innate immune cells such as neutrophils and monocytes, leading to microvascular clot formation a process termed immunothrombosis. This mechanism reflects the complex interaction between innate immunity, endothelial cells, platelets, and the coagulation system. While immunothrombosis may initially serve a protective role, uncontrolled and systemic activation during sepsis can cause thrombotic and hemorrhagic complications, ranging from subtle coagulation abnormalities to severe conditions such as disseminated intravascular coagulation (DIC). Endothelial dysfunction, characterized by glycocalyx breakdown, increased permeability, and proinflammatory as well as procoagulant phenotypes, accelerates the development of immunothrombosis. Future investigations are essential to clarify the underlying mechanisms, identify prognostic biomarkers, establish risk stratification tools, and evaluate novel therapeutic strategies targeting immunothrombosis in sepsis [91].

Targeting Adrenomedullin in Sepsis

Among biomarkers that signal endothelial dysfunction, adrenomedullin (ADM) has emerged as particularly relevant in sepsis. ADM is a vasoactive peptide with both prognostic and potential therapeutic significance. It exerts immunomodulatory effects and stabilizes the endothelial barrier, thereby supporting vascular integrity [92]. Its affinity for vascular endothelium, interstitial tissue, and smooth muscle, combined with its vasodilatory properties, contributes to hypotension and increased vascular permeability in sepsis. At elevated concentrations, ADM induces excessive vasodilation, and high plasma levels have been linked to greater vasopressor requirements, multiorgan failure, and increased mortality [93-95].

Lundberg et al. demonstrated that circulating bioactive ADM (bio-ADM) measured at ICU admission correlates with 30-day mortality and organ dysfunction in both septic patients and the broader ICU population. Elevated bio-ADM was associated with higher vasopressor needs (OR 1.33, 95% CI 1.23–1.42; 95% CI 1.17–1.50). A threshold of 70 pg/mL distinguished survivors from non-survivors, though a Youden's index–derived cut-off of 108 pg/mL provided stronger predictive accuracy. Conversely, reductions in mid-regional pro-adrenomedullin (MR-proADM) levels during ICU stay have been linked to favorable outcomes. Survivors showed a decline to 1.65 nmol/L within 48 hours of admission, with persistently lower levels by day 5 compared to non-survivors. MR-proADM has proven useful in identifying patients at high risk of organ dysfunction, independent of infection source. It also aids clinicians in resource allocation, outperforming PCT, CRP, SOFA scores, and lactate in predicting mortality [97, 98]. From a therapeutic standpoint, ADM represents a potential treatable trait. Adrecizumab (HAM8101), a non-neutralizing anti-ADM antibody targeting the N-terminal region, binds ADM without fully blocking its function. Instead, it reduces excessive interstitial ADM activity, thereby limiting vasodilation while enhancing

circulating ADM's stabilizing effects on endothelial permeability [99]. The AdrenOSS-2 trial, a phase 2a double-blind, randomized, placebo-controlled study, evaluated adrecizumab in septic shock patients with elevated bio-ADM (>70 pg/mL). The antibody was well tolerated, with a favorable safety profile, and although efficacy was not the primary endpoint, improvements in multiorgan dysfunction were observed [100]. Building on these findings, the ENCOURAGE trial (phase IIb/III) is now investigating adrecizumab (4 mg/kg) in septic shock patients immediately after vasopressor initiation, employing both predictive and prognostic enrichment strategies. Its primary goals are to reduce 28-day mortality and improve SOFA scores [96].

Soluble Triggering Receptor Expressed on Myeloid Cells 1 and Sepsis

Among additional biomarkers of interest, the Triggering Receptor Expressed on Myeloid Cells (TREM) family comprises several isoforms with low sequence homology, each containing a single immunoglobulin-like domain. Activation of TREMs initiates intracellular signaling cascades that involve calcium mobilization, cytoskeletal reorganization, and transcription factor activation. Expression of TREMs on effector cell surfaces is markedly increased in tissues, fluids, and skin affected by infections caused by Gram-positive or Gram-negative bacteria as well as fungi [101]. Both TREM and its soluble form have been investigated as diagnostic markers for septic shock [102], prognostic indicators of infection [103], and potential therapeutic targets in sepsis.

Nangibotide, a selective inhibitor of TREM-1, has been developed as a candidate therapy [104]. The phase 2b ASTONISH trial assessed its efficacy, safety, and tolerability in septic shock, with particular attention to patients exhibiting elevated soluble TREM-1 (sTREM-1) levels [105]. Although the primary endpoint-change in SOFA score from baseline to day 5-was not achieved in the overall cohort, exploratory analyses revealed that patients with sTREM-1 concentrations ≥532 pg/mL experienced a significant improvement in ΔSOFA scores at day 5 when treated with high-dose nangibotide. These findings highlight the prognostic relevance of sTREM-1 and underscore the importance of carefully balancing biomarker distributions across study groups when applying single cutoffs for patient selection in future trials.

Thrombocytopenia Associated Multiple Organ Failure in Sepsis

Thrombocytopenia-associated multiple organ failure (TAMOF) represents a clinical phenotype encompassing syndromes driven by widespread microvascular thrombosis, including thrombotic microangiopathies (TMAs), thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), and disseminated intravascular coagulation (DIC). It typically presents as an abrupt decline in platelet counts that rapidly progresses to multi-organ failure in critically ill patients. The thrombocytopenia reflects platelet consumption in the formation of diffuse microvascular clots, which in turn cause tissue ischemia and organ dysfunction. Despite current therapeutic approaches, mortality rates remain high, ranging from 5% to 80% [106].

While pro-thrombotic and anti-fibrinolytic responses are beneficial in localized injury, they become harmful in the context of systemic endothelial damage, manifesting as thrombocytopenia, diffuse thrombosis, and organ failure. Critically ill patients often develop systemic endothelial microangiopathy following diverse insults, and the resulting thrombotic microangiopathies can be classified into three overlapping phenotypes: TTP, consumptive DIC, and non-consumptive secondary TMA [107].

Emerging evidence suggests that nonspecific plasma-based therapies, such as therapeutic plasma exchange (TPE), may help reverse multi-organ failure and improve outcomes in TAMOF. However, the American Society for Apheresis currently assigns TPE in sepsis with MOF a category III recommendation, indicating that its optimal role remains uncertain and decisions should be individualized [108]. At present, no single-agent therapy has proven effective for DIC. Multiple agents-including heparin, antithrombin III, recombinant tissue factor pathway inhibitor, recombinant activated protein C, protein C concentrate, and recombinant soluble thrombomodulin have been tested, but none have demonstrated consistent success [109-110].

Conclusions

Precision medicine in septic shock is an evolving field, with advances in biomarkers, genetics, and clinical tools improving patient stratification and therapeutic decision-making. The growing use of multi-omics, bioinformatics, and machine learning is helping to identify biologically relevant subphenotypes, offering the potential to move beyond a uniform treatment approach toward more individualized care. However, phenotype-based therapies currently lack robust evidence from randomized controlled trials and are not recommended by Surviving Sepsis Campaign guidelines. Standard care—early antibiotics, source control, fluid resuscitation, and vasopressors remains essential for all patients. In selected cases of refractory septic shock with high mortality risk, tailored approaches such as immunomodulation or blood purification may be considered in specialized settings. Clinical implementation remains gradual due to overlapping and dynamic phenotypes, shared hemodynamic needs, and practical limitations such as cost and limited access to rapid diagnostics. Despite these challenges, the overarching goal is to deliver the right therapy to the right patient at the right time, improving survival and reducing the burden of sepsis.

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