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REVIEW

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Update on sepsis treatment

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Abstract

Sepsis and septic shock remain a global health challenge with high mortality and long-term morbidity. Contemporary evidence highlights immune dysregulation, endothelial dysfunction, and glycocalyx degradation as key pathophysiological drivers. Clinical management has evolved from uniform approaches to precision-guided strategies that integrate subphenotyping, biomarkers and novel therapies. This review synthesizes data from guidelines, translational research, and clinical trials to provide a comprehensive perspective on current management and future directions in sepsis care.

Keywords Septic shock, Refractory septic shock, Hemoadsorption, Polymyxin B, Catecholamine-resistant hypotension

Background

Sepsis remains a leading cause of morbidity and mortality worldwide despite substantial advances in supportive care and antimicrobial therapy [1]. Over the past decades, international guidelines [2] have standardized key aspects of management, including early recognition, prompt antimicrobial administration, source control, and hemodynamic resuscitation. While these strategies have improved outcomes, mortality from septic shock remains high, highlighting the limitations of current treatment approaches.

Increasing evidence suggests that sepsis is not a single disease entity but rather a highly heterogeneous syndrome characterized by dysregulated host responses to infection. Patients with sepsis exhibit substantial variability in immune activation, endothelial dysfunction, coagulation abnormalities, and metabolic responses. This biological heterogeneity may partly explain why many therapeutic interventions targeting specific pathophysiological pathways have failed to demonstrate consistent benefit in unselected patient populations.

Consequently, there is growing interest in precision medicine approaches aimed at identifying clinically meaningful subphenotypes or "treatable traits" within the broader sepsis population. Advances in biomarker profiling, transcriptomics, and multimodal clinical monitoring are increasingly enabling the identification of patient subgroups with distinct biological signatures and potentially differential responses to therapy.

In this context, the present review summarizes recent insights into sepsis pathophysiology and discusses emerging therapeutic strategies, with particular emphasis on biomarker-guided interventions and precision medicine approaches that may help individualize treatment and improve outcomes in patients with sepsis.

This review integrates updated insights into sepsis pathophysiology, clinical management, and emerging therapeutic strategies. By combining guideline recommendations, translational studies, and landmark clinical trials, it outlines the rationale for a precision medicine approach that tailors interventions to immune

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and endothelial profiles, paving the way for improved patient outcomes (Fig. 1).

Table 1 provides a conceptual framework linking major treatable traits in sepsis to corresponding biomarker signatures and potential therapeutic strategies. It is intended as a biological and clinical map rather than a prescriptive treatment algorithm, illustrating how distinct pathophysiological profiles may inform personalized adjunctive interventions.

Pathophysiology of sepsis

Understanding the biological rationale for phenotype-oriented management requires an appreciation of the fundamental pathophysiological processes underlying sepsis. These processes are not uniform across patients and involve variable contributions from immune dysregulation, endothelial injury, and metabolic failure.

Dysregulated host response

Sepsis arises from a maladaptive host response to infection in which hyperinflammation coexists with immune suppression. Pathogen-associated and damage-associated molecular patterns (PAMPs and DAMPs) activate pattern recognition receptors, leading to an uncontrolled release of cytokines, activation of coagulation pathways, and cellular injury. At the same time, compensatory mechanisms produce immune exhaustion and apoptosis of lymphocytes, resulting in increased susceptibility to secondary infections and viral reactivation [3, 4]. The coexistence of these opposing responses explains the heterogeneity of clinical trajectories in sepsis.

Extracellular histones as DAMPs

Extracellular histones, released during neutrophil extracellular trap formation and cell death, act as potent DAMPs in sepsis. They induce endothelial cytotoxicity, activate coagulation, and propagate systemic inflammation [5]. Elevated circulating histone levels have been proposed as biomarkers for diagnosis, severity assessment, and prognosis in critically ill patients. Therapeutic strategies targeting histone neutralization may represent future avenues for mitigating endothelial injury.

Immune dysfunction and subphenotypes

Immune dysfunction in sepsis encompasses a spectrum of biologically distinct subphenotypes rather than a

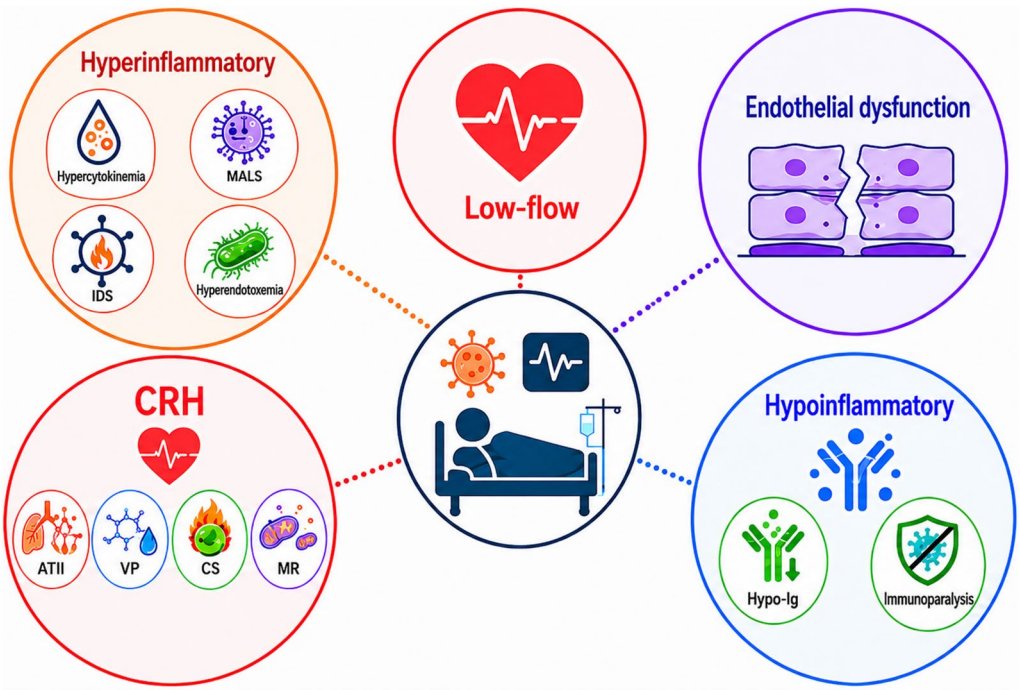

Fig. 1 Conceptual framework illustrating a phenotype-driven approach to sepsis management based on the identification of biologically distinct endotypes. Patients with sepsis exhibit heterogeneous host responses that can be characterized using clinical features, biomarkers, and immunological profiling. These endotypes may define specific treatable traits, including hyperinflammation, endotoxemia, immune suppression, vasoplegia, or metabolic dysfunction. Identification of these biological signatures may enable targeted therapeutic strategies, such as immunomodulatory therapies (e.g., IL-1 blockade), endotoxin removal, cytokine modulation, or hemodynamic interventions tailored to the underlying pathophysiology. This approach moves beyond traditional "one-size-fits-all" management toward biomarker-guided precision medicine, aiming to improve patient selection for emerging therapies and enhance clinical outcomes in sepsis.

Table 1 Integrative framework of sepsis treatable traits, biomarker signatures, and precision therapies

Treatable trait	Description	Biomarker	Treatment
Hyperinflammatory phenotype	High endotoxemic phenotype	EAA 0.6–0.9	Endotoxin hemoadsorption devices (e.g., Toraymyxin®)
	High cytokine phenotype	IL-6 plasmatic concentration, however *there is still no threshold plasma cytokine level used for beginning or closure of therapy*	Cytokine hemoadsorption devices (e.g., Cytosorb®)
	High EAA and high cytokine phenotype	Same thresholds as above	Sequential hemoadsorption *Endotoxin hemoadsorption with PMX, Toraymyxin®, and subsequent cytokine hemoadsorption with Cytosorb® has been applied in highly selected patients. Sequential hemoadsorption is intended to remove the primary stimulus that induces the dysregulated inflammatory response*
	Macrophage activation-like syndrome (MALS)	Ferritin > 4420 ng/mL	Anti-IL1 (anakinra) Anti-TNFα TPE in select cases
	Interferon-gamma-driven sepsis (IDS)	IFNγ > 3 pg/ml ≥ 8000 HLA-DR receptors on CD45/CD14-monoytes CXCL9 more than 2200 pg/ml	Anti–IFN-γ–modulating therapies (emapalumab) (investigational)
Hypoinflammatory phenotype	Hypogammaglobulinemia: *polyvalent IVIG immunoglobulins are a logical approach to modulating both pro- and anti-inflammatory responses in sepsis*	IgG < 500 mg/dL or 2 standard deviations below reference values for age	Polyvalent IVIG IgM and IgA-enriched polyclonal IVIG dose of 250 mg/kg/d by a 10-h infusion, for 3 consecutive days
	Immunoparalysis T-cell exhaustion syndrome	Ferritin < 4420 ng/mL HLA-DR < 5000	rhIFNγ Checkpoint inhibitors (e.g., Nivolumab)
Catecholamine-resistant hypotension (CRH)[a]	Vasopressin (VP)	NE > 0.25–0.5 mcg/kg/min	VP infusion and titration
	Angiotensin-II (Ang II)	Renin plasmatic concentrations (> 172.3 pg/ml) Catecholamine equivalent dose of > 0.25 µg/kg/min for a minimum of 6 h	Ang II infusion and titration
	Corticosteroids	Catecholamine equivalent dose of > 0.25 µg/kg/min for a minimum of 6 h	Hydrocortisone: 100mg single dose followed by 200mg/day
	Metabolic resuscitation: *impairment of mitochondrial function leads to an elevation in reactive oxygen and nitrogen species, causing alterations in vascular tone and heightened capillary permeability, along with a certain degree of resistance to the effects of catecholamines*	Catecholamine equivalent dose of > 0.25 µg/kg/min for a minimum of 6 h Ascorbic acid plasmatic concentrations	Ascorbic acid 1500mg/6h/15 doses plus Thiamine 200mg/12h plus Hydrocortisone (100mg single dose followed by 200mg/day)
Low-flow phenotype	Patients with septic cardiomyopathy exhibiting signs of inadequate perfusion despite the administration and titration of vasoactive drugs (dobutamine) and receiving supportive treatment guided to other phenotypes	Lactate plasmatic concentrations and ΔLactate $ScvO_2$ < 70mmHg $\Delta AvCO_2$ > 6mmHg Echocardiographic parameters	Veno-arterial ECMO

Table 1 (continued)

Treatable trait	Description	Biomarker	Treatment
Endothelial dysfunction	Endothelial cells amplify the immune response and activate the coagulation system. They are both a target and source of inflammation and serve as a link between local and systemic immune responses	BioADM (> 108 pg/mL) MR-proADM (decline in blood plasma concentration to 1.65 nmol/L within 48 h of admission) Syndecan-1 (glycocalyx) sTM-soluble thrombomodulin (deep endothelial injury) Angiopoietin-2 / Angiopoietin-1 Ang-2/Ang-1 ratio Tie-2 (↓ in endothelial dysfunction) VWF ↑ and ADAMTS-13 ↓ Soluble VE-cadherin S1P (sphingosine-1-phosphate) Selectins: E-selectin, P-selectin Adhesion molecules: ICAM-1, VCAM-1 Extracellular histones Endothelial and leukocyte-derived microvesicles Direct assessment of glycocalyx and microcirculation: PBR (perfused boundary region) MFI (microvascular flow index) Proportion of perfused vessels	Future research Albumin infusion (endothelial stabilizing effect), adrecizumab (anti-ADM; investigational) Monoclonal antibodies (Nivolumab)
	Resuscitation-associated endotheliopathy Resuscitation-induced deterioration of endothelial integrity	Post-bolus syndecan-1 elevation Post-resuscitation soluble thrombomodulin (sTM) increase Increased PBR (indicative of glycocalyx degradation) Reduced MFI (impaired microvascular flow)	Avoid unnecessary rapid fluid boluses Limit initial fluid volume Prefer early initiation of vasopressors Microcirculatory monitoring (SDF imaging)
	Immunothrombosis: procoagulant and microthrombotic state with risk of DIC	Thrombocytopenia Elevated D-dimer TAT complexes (thrombin–antithrombin) FDPs (fibrin degradation products) Prolonged PT and aPTT NETs (extracellular histones, cell-free DNA, MPO–DNA complexes) Increased VWF/decreased ADAMTS13	TPE Tailored coagulation management rTM (soluble thrombomodulin) Complement inhibitors (experimental: C5a and C3a blockade)
	Thrombocytopenia-associated multiple organ failure (TAMOF)	Thrombotic microangiopathies (TMAs) Thrombotic thrombocytopenic purpura/hemolytic uremic syndromes (TTP/HUS) Disseminated intravascular coagulation (DIC)	TPE Heparin, antithrombin III, recombinant tissue factor pathway inhibitor, recombinant activated protein C, protein C concentrate and recombinant soluble thrombomodulin

aPTT: activated partial thromboplastin time, Ang II: angiotensin II, BioADM: bioactive adrenomedullin, CD45/CD14: monocyte markers used for HLA-DR quantification, CRH: catecholamine-resistant hypotension, CXCL9: C-X-C motif chemokine ligand 9, $\Delta AvCO_2$: arteriovenous carbon dioxide difference, ΔLactate: change in lactate or lactate clearance, DIC: disseminated Intravascular Coagulation, ECMO: extracorporeal membrane oxygenation, EAA: endotoxin activity assay, FDPs: fibrin degradation products, HLA-DR: human leukocyte antigen DR, HUS: hemolytic uremic syndrome, ICAM-1: intercellular adhesion molecule-1, ICU: intensive care unit, IDS: interferon-gamma-driven sepsis, IFN-γ: interferon gamma, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, IL-6: interleukin 6, IL-10: interleukin 10, IVIG: intravenous immunoglobulin, MALS: macrophage activation-like syndrome, MFI: microvascular flow index, MODS: multiple organ dysfunction score, MPO–DNA: myeloperoxidase–DNA complexes, MR-proADM: mid-regional proadrenomedullin, NE: norepinephrine, NETs: neutrophil extracellular traps, PBR: perfused boundary region, PMX: polymyxin B, PMX-HA: polymyxin B hemoadsorption, PT: prothrombin time, RCT: randomized controlled trial, rhIFN-γ: recombinant human interferon gamma, rTM: recombinant thrombomodulin, S1P: sphingosine-1-phosphate, sTM: soluble thrombomodulin, $SvcO_2$: central venous oxygen saturation, SOFA: Sequential Organ Failure Assessment, TAMOF: Thrombocytopenia-Associated Multiple Organ Failure, TAT complexes: thrombin–antithrombin complexes, TMA: thrombotic microangiopathy, TPE: therapeutic plasma exchange, TTP: thrombotic thrombocytopenic purpura, VCAM-1: vascular cell adhesion molecule-1, VE-cadherin: vascular endothelial cadherin, VWF: von Willebrand Factor

single continuum of severity. These immune endotypes are characterized by divergent inflammatory trajectories, temporal dynamics, and clinical outcomes, providing a mechanistic explanation for the heterogeneous responses observed across therapeutic interventions.

Immune profiling has identified distinct subphenotypes in sepsis. Macrophage activation-like syndrome (MALS) is characterized by hyperferritinemia, overwhelming inflammation, and high mortality [6, 7]. In contrast, immunoparalysis is defined by reduced monocyte HLA-DR expression and impaired antigen presentation, associated with recurrent infections and late mortality [8]. Recent studies have also described metabolic subphenotypes and transcriptomic signatures that stratify patients into hyperinflammatory and hypoinflammatory clusters with different responses to therapy [9–11]. Such subphenotyping paves the way for immunotherapy tailored to patient-specific immune trajectories [12].

One of the most recent advancements in this regard is the proposal put forward by Giamarellos-Bourboulis et al. [13] in a large multicenter cohort study where they identified interferon-gamma-driven sepsis (IDS) as a newly defined and clinically significant endotype. Analyzing 5503 patients from 14 European cohorts, the authors investigated whether IFNγ-induced production of the cytotoxic chemokine CXCL9 reflects a distinct pathophysiological mechanism. Using discovery-set analyses, they determined that IFNγ > 3 pg/mL and CXCL9 > 2200 pg/mL optimally predicted mortality, establishing these thresholds as diagnostic criteria for IDS. IDS occurred in approximately 20% of all patients in both discovery and validation cohorts, demonstrating strong reproducibility. Biologically, IDS represents a macrophage-activated but non-MALS endotype characterized by disproportionately high CXCL9 levels. Overlap with MALS was < 1%, supporting mechanistic distinctness. Clinically, IDS conveyed high 28-day mortality (~ 40–43%), second only to MALS, and remained an independent predictor of death after adjustment for comorbidities, severity scores, infection types, and pathogens. Dynamic analyses showed that declines in IFNγ and CXCL9 during the first 72 h correlated with improved survival, whereas persistent CXCL9 elevation marked non-survivors. The study establishes IDS as a robust new sepsis endotype with implications for precision immunotherapy. Currently, a clinical trial (The EMBRACE Trial, NCT06694701) is evaluating the efficacy of emapalumab in this condition.

Endothelial injury and glycocalyx degradation

Endothelial dysfunction is a hallmark of sepsis, driving vascular leakage, tissue edema, and organ failure. The shock-induced endotheliopathy (SHINE) model emphasizes the role of glycocalyx shedding, microvascular thrombosis, and dysregulated barrier function. Circulating biomarkers including syndecan-1, soluble VE-cadherin, and sphingosine-1-phosphate have been correlated with adverse outcomes [14]. Albumin has been shown to preserve endothelial integrity by reducing VE-cadherin phosphorylation and mitigating glycocalyx damage [15]. Thus, the endothelial surface layer represents both a pathophysiological nexus and a therapeutic target.

The interplay between inflammation, endothelial dysfunction, and coagulation represents a central component of sepsis pathophysiology. In this context, the protein C pathway [16] plays a pivotal regulatory role by exerting anticoagulant, anti-inflammatory, and cytoprotective effects. In patients with sepsis, reduced endogenous protein C levels have been consistently associated with an increased risk of organ dysfunction and mortality. Recent evidence suggests that monitoring protein C activity may help identify patients with sepsis-induced coagulopathy or disseminated intravascular coagulation who could potentially benefit from targeted therapeutic strategies. Although supplementation strategies remain investigational, these findings reinforce the concept that coagulation pathways represent a potential target for precision medicine approaches in sepsis.

Vasoplegia in sepsis

Septic shock is often dominated by vasoplegia, characterized by reduced vascular tone and catecholamine hyporesponsiveness. Mechanisms include excessive nitric oxide production, prostanoid imbalance, impaired vascular smooth muscle signaling, and degradation of the glycocalyx [17]. Vasoplegia not only contributes to refractory hypotension, but also exacerbates microcirculatory dysfunction. Recognizing vasoplegic shock as a distinct pathophysiological entity supports the rationale for individualized hemodynamic targets and adjunctive therapies such as vasopressin, angiotensin II (Ang II), or hemoadsorption (HA) in refractory states.

Clinical management

Recognition of sepsis heterogeneity has important implications for clinical management. While early source control, antimicrobial therapy, and hemodynamic stabilization remain foundational, these measures alone may be insufficient in patients with profound immune or endothelial dysregulation. Consequently, standard-of-care interventions should be viewed as a baseline upon which phenotype-aligned adjunctive strategies may be layered.

Hemodynamic resuscitation: catecholamine-resistant hypotension

Vasoplegia represents a pathophysiologically distinct component of septic shock, reflecting the interplay between endothelial dysfunction, impaired vascular smooth muscle responsiveness, and dysregulated neurohumoral signaling. Recognition of vasoplegic shock as a specific phenotype provides the rationale for individualized hemodynamic targets and tailored vasopressor strategies.

Among patients with vasodilatory shock, there is significant heterogeneity of RAAS endotype. Currently, Ang II should not be considered as a first-line agent, but having demonstrated its safety and physiological efficacy, it may have a role as a vasopressor adjuvant. Ang II is a natural hormone with endocrine properties, autocrine and paracrine effects recently approved for the treatment of distributive shock, thus it has vasoconstrictor effects at both arterial and venous levels [18]. Firstly, data from a study by Chawla et al. [19] support the safety and efficacy of Ang II in the treatment of patients with "Catecholamine Resistant Hypotension" (CRH). In the ATHOS-3 trial [20] 344 patients refractory to catecholamine treatment with norepinephrine (0.2 μg/kg/min or equivalent) were randomized to receive Ang II or placebo. The main objective of the study was to achieve an increase in baseline MAP ≥ 10 mmHg or raise arterial pressure > 75 mmHg; this was achieved in 69.9% of Ang II patients and in 23.4% of the placebo group without significant differences in side effects. Even Wieruszewski et al. [21] performed an exploratory post hoc analysis of ATHOS-3 trial and concluded that initiation of Ang II at a low norepinephrine equivalent dose (NED) of ≤ 0.25 μg/kg/min was associated with higher likelihood of survival when compared to placebo. Post hoc subgroup analyses of the ATHOS-3 trial have provided additional data to show that patients on renal replacement therapy (RRT) at randomization had better rates of recovery to RRT independence at day seven and improved survival with Ang II [22] and that patients with an angiotensin I/II (Ang I/II) ratio below the median were significantly more likely to survive (suggesting a degree of ANG II deficiency) [23].

Coloretti et al. [24] showed that the therapeutic role of Ang II in distributive shock appears most pronounced within biologically distinct phenotypes characterized by dysregulation of the renin–angiotensin–aldosterone axis. The identified responsive clusters include patients exhibiting marked hyperreninemia, indicative of endogenous Ang II deficiency or receptor desensitization; in fact, Bellomo et al. [25] observed that renin levels are markedly elevated in vasodilatory shock and could identify patients in whom treatment with Ang II may be more beneficial; those with acute kidney injury requiring or at risk for renal replacement therapy, in whom selective efferent arteriolar vasoconstriction may augment glomerular filtration and renal recovery; and individuals with acute respiratory distress syndrome, a condition associated with pulmonary endothelial ACE depletion and impaired Ang II generation. Clinical benefit is maximized when Ang II is integrated early within a multimodal vasopressor regimen, particularly at low-to-moderate norepinephrine equivalents (< 0.3 μg/kg/min), reflecting a precision hemodynamic approach tailored to pathophysiologic subtypes of vasoplegia.

Immunomodulatory therapies

Immunotherapy for sepsis is an evolving field. Targeted agents such as nangibotide [26], a TREM-1 pathway inhibitor (Triggering Receptor Expressed on Myeloid Cells), and adrecizumab [27], a non-neutralizing anti-adrenomedullin antibody, have demonstrated safety and biological activity, particularly in biomarker-enriched populations. Trials underscore the importance of patient selection, as benefits are most pronounced in subsets defined by immune and endothelial biomarkers. Future directions include immune checkpoint inhibitors and cytokine-targeted strategies.

Slim et al. [28] conducted a systematic search of major databases up to January 2024, identifying 771 relevant studies, including 489 interventional trials and 282 observational studies evaluating a wide spectrum of immunomodulatory interventions. These therapies targeted multiple pathways involved in sepsis pathogenesis, including modulation of the innate immune response, complement system, coagulation and endothelial dysfunction, as well as immune stimulation strategies such as cytokines, growth factors, intravenous immunoglobulins, mesenchymal stem cells, and immune checkpoint inhibitors. Only a minority of studies (approximately 9%) incorporated a personalized treatment approach based on biomarker-guided patient stratification or identification of specific subphenotypes. Many clinical trials have produced inconsistent or negative results, which may partly reflect the heterogeneity of sepsis and the limitations of "one-size-fits-all" therapeutic strategies. Emerging evidence suggests that targeted therapies may demonstrate clinical benefit when applied to carefully selected patient subgroups defined by immune profiles or biomarker signatures.

Anakinra

Interest in IL-1 receptor blockade for septic shock has re-emerged as advances in immunophenotyping have revealed that sepsis comprises biologically distinct endotypes rather than a uniform entity. Although the original phase III trials of recombinant IL-1 receptor antagonist

(IL-1ra) in severe sepsis failed to demonstrate mortality benefit in unselected populations, they established the mechanistic rationale for targeting IL-1-driven hyperinflammation [29, 30]. Subsequent reanalyses of these datasets identified a subgroup of patients with hepatobiliary dysfunction and coagulopathy who experienced a substantial survival advantage when treated with anakinra [31]. These findings have shifted the therapeutic paradigm toward precision immunotherapy, whereby IL-1 blockade is applied selectively to patients with hyperinflammatory phenotypes rather than broadly across all septic shock presentations [32]. The PROVIDE trial operationalized this strategy by assigning anakinra specifically to patients with biomarker-defined MALS, demonstrating the feasibility and biological coherence of endotype-guided IL-1 inhibition in sepsis [33]. Collectively, these data suggest that anakinra may hold significant therapeutic potential in septic shock when deployed within an endotype-driven framework. More recently, the ImmunoSep trial [34] has been published, evaluating a biomarker-guided precision immunotherapy strategy in patients with Sepsis-3-defined sepsis associated with pneumonia (community-acquired, hospital-acquired, or ventilator-associated) or bacteremia. Patients were stratified according to immune endotype using ferritin and monocyte HLA-DR expression to identify either macrophage activation-like syndrome (MALS) or sepsis-induced immunoparalysis (SIP). MALS was defined by ferritin > 4420 ng/mL, whereas SIP was defined by ferritin ≤ 4420 ng/mL with < 5000 HLA-DR receptors on CD45/CD14 monocytes. Participants were randomized to standard care plus precision immunotherapy or standard care plus placebo. Patients with MALS received intravenous anakinra, while those with SIP received subcutaneous recombinant human interferon-γ; matched placebos were administered using a double-dummy design for up to 15 days. The primary endpoint was improvement in organ dysfunction, defined as a ≥1.4-point reduction in mean Sequential Organ Failure Assessment (SOFA) score by day 9. Among 276 patients included in the primary analysis (mean age 70 ± 13 years; baseline median SOFA 9), the primary endpoint occurred in 35.1% of patients receiving precision immunotherapy versus 17.9% receiving placebo (absolute difference 17.2%, 95% CI 6.8–27.2; $P = 0.002$). 28-day mortality did not differ significantly between groups.

Interferon

Interferon-γ (IFN-γ) occupies a paradoxical and increasingly central position in contemporary immunopathological models of septic shock, functioning both as a driver of early hyperinflammatory injury and as a potential therapeutic agent in late immunoparalysis. In the hyperacute phase of shock, excessive IFN-γ secretion by NK cells, Th1 lymphocytes, and activated macrophages amplifies downstream cytotoxic programs, notably through induction of the chemokine CXCL9, which is uniquely stimulated by IFN-γ and exerts potent pro-apoptotic and endothelial-injuring effects. IFN-γ–induced CXCL9 augments tissue injury, drives leukocyte recruitment, and promotes apoptosis in endothelial and parenchymal cells, contributing to multiorgan dysfunction. [35–37]. This mechanism was recently delineated in multicohort analysis identifying an IFN-γ-driven sepsis endotype (IDS), defined by circulating IFN-γ > 3 pg/mL and CXCL9 > 2200 pg/mL, present in approximately 20% of Sepsis-3 patients and independently associated with 40–43% 28-day mortality [24]. Conversely, in the immunosuppressive phase of sepsis—marked by profound monocytic HLA-DR downregulation, impaired cytokine production, and defective microbial clearance—endogenous IFN-γ becomes insufficient, and its absence correlates with secondary infections and refractory shock [38]. Clinical translational data mirror these observations: a multicenter series demonstrated that exogenous IFN-γ administration in sepsis-induced immunosuppression restored monocyte HLA-DR expression, improved antimicrobial effector functions, and enhanced pathogen clearance without major safety concerns [39]. Complementary preclinical work shows that IFN-γ reverses sepsis-associated immunoparalysis by reprogramming dendritic cell metabolism toward glycolytic activation via PI3K/AKT/mTOR signaling, thereby restoring immunostimulatory capacity [40]. Therapeutically, these findings imply a dual strategy: inhibition of the IFN-γ/CXCL9 axis may benefit patients with IDS-like hyperinflammation, whereas targeted administration of IFN-γ may be advantageous in biomarker-confirmed immunoparalysis. Thus, IFN-γ emerges as a bidirectional immunoregulatory tool whose quantification and kinetics should guide precision immunotherapy in septic shock.

Nangibotide

The TREM family comprises several isoforms characterized by low inter-member sequence homology and the presence of a single immunoglobulin-like domain. Engagement of TREM receptors initiates intracellular signaling cascades that result in calcium mobilization, actin cytoskeleton reorganization, and activation of transcription factors. Surface expression of these receptors on effector cells is markedly upregulated in the skin, biological fluids, and tissues during infections caused by Gram-positive bacteria, Gram-negative bacteria, and fungi [41]. TREM and its soluble part, serve as a diagnosis of septic shock [42] and as a prognostic marker of infection [43] and as a target molecule for adjuvant treatment of sepsis.

Nangibotide is an inhibitor of TREM-1 [44]. A phase 2b clinical trial, ASTONISH, evaluated its efficacy, safety, and tolerability in patients with septic shock, specially focused on the high sTREM-1 subgroup and its inhibition properties (ClinicalTrials.gov Identifier NCT04055909) [26]. However, the primary endpoint, defined as the change in total SOFA score from baseline to day 5, was not achieved in the overall study population. In prespecified exploratory analyses restricted to patients with sTREM-1 concentrations ≥ 532 pg/mL, a statistically significant improvement in the day-5 ΔSOFA score was observed, favoring high-dose nangibotide. Given the prognostic relevance of sTREM-1, future studies employing a single biomarker cutoff for patient selection should ensure that study arms exhibit balanced distributions of absolute sTREM-1 concentrations to minimize potential confounding effects.

Adrecizumab

Among biomarkers reflecting endothelial dysfunction, adrenomedullin (ADM) has attracted particular interest. ADM is a vasoactive peptide hormone with reported prognostic relevance and potential therapeutic implications in sepsis. It exerts immunomodulatory effects and contributes to stabilization of the endothelial barrier, thereby helping to preserve vascular integrity [45]. Its tropism for vascular endothelium, interstitial tissues, and smooth muscle, together with its vasodilatory properties, may contribute to sepsis-associated hypotension and increased vascular permeability. At elevated concentrations, ADM can induce excessive vasodilation, and increased circulating levels have been associated with greater vasopressor requirements, multiorgan dysfunction, and increased mortality [46–48]. Lundberg et al. [49] concluded that circulating bioactive adrenomedullin (bio-ADM) on admission is associated with 30-day mortality and organ failure in sepsis patients as well as in a general intensive care unit (ICU) population. Elevated bio-ADM was associated with an increased need of vasopressors, OR 1.33 (95% CI 1.23–1.42) (95% CI 1.17–1.50) and even a cutoff of 70 pg/mL differentiated between survivors and non-survivors in sepsis, but a Youden's index derived threshold of 108 pg/mL performed better.

Conversely, several studies have reported that a more pronounced reduction in MR-proADM (mid-regional pro-adrenomedullin) levels during the ICU stay is associated with favorable clinical outcomes. Survivors typically demonstrate a decrease in plasma concentrations to approximately 1.65 nmol/L within 48 h of admission, with levels remaining consistently lower by day 5 compared with non-survivors. The potential of MR-proADM for the early identification of patients at high risk of organ dysfunction has been evaluated independently of the infection source. Moreover, MR-proADM has been proposed as a tool to support clinical decision-making regarding hospital and ICU resource allocation, as it shows superior predictive performance for mortality compared with procalcitonin (PCT), C-reactive protein (CRP), SOFA score, and lactate [50, 51].

As a potential treatable trait, adrenomedullin (ADM) has been targeted therapeutically with adrecizumab (HAM8101), a non-neutralizing monoclonal antibody against ADM with epitope specificity for the N-terminal region of the peptide. By binding to ADM, adrecizumab does not completely inhibit its biological activity; rather, it attenuates ADM-mediated second-messenger signaling. This mechanism may reduce excessive vasodilation by sequestering high levels of ADM present in the interstitial compartment, while increasing the effective activity of circulating ADM, which may contribute to stabilization of endothelial permeability. The AdrenOSS-2 study, a phase IIa, double-blind, randomized, placebo-controlled, biomarker-guided clinical trial, evaluated the safety and tolerability of adrecizumab in patients with septic shock and elevated plasma concentrations of biologically active ADM (> 70 pg/mL) [27]. Adrecizumab was well tolerated and showed a favorable safety profile. Although it was not the primary objective of the study, an improvement in multiorgan dysfunction was observed. A subsequent study, the ENCOURAGE study, is a phase IIb/III clinical trial that will assess adrecizumab (4 mg/kg) in septic shock patients immediately after initiation of vasopressors. Interestingly, this study combines predictive and prognostic enrichment strategies with the primary objective of reducing 28-day mortality and the SOFA score.

Extracorporeal blood purification in the hyperinflammatory phenotype

In a subset of patients, sepsis is characterized by extreme inflammatory or endotoxin-driven dysregulation that persists despite optimized conventional therapy. In this context, extracorporeal blood purification techniques have been proposed as adjunctive, phenotype-oriented interventions aimed at modulating upstream pathophysiological drivers rather than replacing standard supportive care.

Hyperinflammation with high cytokine phenotype: cytokine hemoadsorption

The use of HA therapy as a personalized therapy may be considered in a situation of septic shock and multiorgan dysfunction refractory to standard treatment. CytoSorb® therapy may be of benefit in conditions characterized by excessive cytokine release because the device effectively attenuates circulating cytokine concentrations during

systemic inflammation in humans in vivo [52]. Other devices have been also studied. HA330 hemoperfusion has shown promising results [53]. Also therapeutic plasma exchange (TPE) can remove inflammatory mediators and benefit patients, but there is still a path to traverse [54]. So, cytokine HA may have a role as a therapy in a particular subgroup of patients with severe septic shock, hyperlactatemia, multiorgan failure, and very high hypercytokinemia [55]. Recently, *best practice* criteria have been released for initiating hemoadsorptive therapy in cases of septic/vasoplegic shock that do not respond to standard care and exhibit significantly elevated soluble markers of inflammation and also the therapy should commence within 12 h of the diagnosis of septic/vasoplegic shock but no later than 24 hours [56]. However, to date, no specific threshold plasma cytokine level has been established to guide the initiation or discontinuation of therapy. Among the studies published so far in which HA has been used in patients with distributive shock, it is particularly important to distinguish those involving patients with sepsis and those reporting plasma interleukin-6 (IL-6) concentrations. Some studies have documented IL-6 plasma levels—some utilizing them as inclusion criteria, while others reporting them solely for informational purposes.

Severe hypercytokinemia is an early and often underrecognized feature in patients with sepsis, representing the most extreme end of the hypercytokinemia spectrum. Clinically, it is characterized by refractory septic shock, multiple organ dysfunction, and a markedly high mortality rate.

In such cases, blood purification techniques may attenuate the inflammatory response through a rapid and broad reduction of circulating cytokines, potentially leading to improved patient survival [57].

A novel paradigm in endotoxin hemoadsorption?

The TIGRIS trial [58] provides Bayesian evidence supporting the benefit of polymyxin B HA (PMX) in biomarker-defined endotoxic septic shock, demonstrating reduced 28-day mortality (OR 0.67) and consistent survival benefit compared with prior EUPHRATES [59] findings. Notably, the effect was sustained at 90 days, with greater mortality reduction (OR 0.54) and a number needed to treat of 8.1, supporting the durability of PMX effects in selected patients.

Complementary data from Ruiz-Rodríguez et al. show that endotoxin HA in patients with refractory septic shock and extreme endotoxemia (EAA $\geq$ 0.9) significantly reduces endotoxin levels and improves hemodynamic stability, although mortality remains high. These findings further support a biomarker-guided, precision-medicine approach to identifying patients who may benefit from endotoxin-targeted therapies.

Sequential hemoadsorption

In sepsis and septic shock, endotoxemia (presence of endotoxins in the bloodstream) and excessive production of inflammatory mediators, known as a cytokine storm, play a crucial role in the severity of the condition and its prognosis. The goal of sequential HA is to target both endotoxins and cytokines to restore immune homeostasis and alleviate the dysregulated inflammatory response. Current practice has shown that HA helps recovery of immune homeostasis. However, in particular patients, endotoxin-only adsorption may be insufficient [60]. Endotoxemia and the overproduction of inflammatory mediators, in the form of a cytokine storm, are associated with the severity of sepsis and septic shock and determine prognosis [61]. Sequential HA (endotoxin HA with PMX, Toraymyxin®, and subsequent cytokine HA with Cytosorb®) has been applied in highly selected patients [62]. Precision medicine has allowed for a better selection of individuals according to their phenotypic profile to identify patients who could benefit from sequential hemoadsorption (cytokine and endotoxin HA). Sequential HA is intended to remove the primary stimulus that induces the dysregulated inflammatory response. The candidates for sequential HA could be patients with refractory septic shock, multiorgan dysfunction, high endotoxemia, and hypercytokinemia (extremely high levels of IL-6). Real-time monitoring of plasma cytokines (IL-6, IL-10) can guide clinicians to withhold therapy [63].

Safety considerations and unintended adsorption

Beyond potential benefits, HA therapies require careful consideration of procedure-related risks and biological limitations [64]. In PMX hemoperfusion, treatment delivery may be affected by extracorporeal circuit complications and early interruption, most commonly due to circuit coagulation, resulting in incomplete delivery of planned treatment sessions in some clinical series. Moreover, clinical benefit appears heterogeneous across patient populations; subgroups outside the proposed endotoxin "therapeutic window" may fail to improve, and an excessively high endotoxin burden has been suggested as a potential explanation for the lack of benefit in certain patients, underscoring the need for cautious interpretation in very high EAA strata.

Another important limitation of HA—particularly with broad-spectrum sorbent cartridges—is the limited molecular selectivity of these techniques. This may lead to unintended removal of biologically relevant mediators or concomitant pharmacological agents, including

antimicrobials, potentially reducing circulating drug concentrations and affecting treatment efficacy. Experimental and clinical observations indicate that relevant adsorption of several antibiotics may occur [65], supporting the use of therapeutic drug monitoring and dose adjustment when extracorporeal adsorption therapies are applied. In addition, randomized trials and meta-analyses have produced heterogeneous and often inconclusive results, with overall low certainty of evidence regarding outcome benefits, highlighting the importance of careful patient selection and further prospective investigation.

Future perspectives

The future of sepsis research and management lies in the integration of biological subphenotyping with targeted therapeutic strategies. Advances in multi-omic technologies and real-time biomarker assessment offer the opportunity to refine patient stratification and move from protocolized uniformity toward true precision medicine in critical care.

Precision medicine and theragnostics

The future of sepsis management lies in precision medicine. High-throughput technologies have enabled the identification of transcriptomic, proteomic, and metabolomic signatures that classify patients into biologically distinct groups. Theragnostics, combining diagnostic biomarkers with tailored therapies, represents a major opportunity to deliver the right intervention to the right patient at the right time [66].

Subphenotyping and biomarkers

Subphenotyping has reshaped the understanding of sepsis heterogeneity. Immune clusters such as hyperinflammatory and hypoinflammatory endotypes show differential responses to interventions [21]. Similarly, metabolic subphenotypes of septic shock demonstrate variable stability and prognostic impact [67]. Biomarkers including ferritin, monocyte HLA-DR, soluble VE-cadherin, syndecan-1, and circulating histones offer insight into immune and endothelial dysfunction, while emerging platforms integrate multi-omic data to refine patient stratification [68].

Personalized hemodynamic targets

Hemodynamic resuscitation strategies are evolving toward personalization. Instead of fixed targets for mean arterial pressure and fluid administration, individualized goals based on comorbidities, vascular physiology, and endothelial status are gaining traction [69]. Dynamic and multimodal monitoring enables titration of fluids and vasopressors to optimize perfusion while limiting iatrogenic harm. Personalized resuscitation may bridge the gap between guideline-based care and patient-specific physiology.

Operationalizing precision medicine in sepsis: a bedside roadmap

Implementing precision medicine in sepsis requires translating biological heterogeneity into actionable bedside decisions. Table 1 provides a pragmatic framework to operationalize precision medicine in sepsis by linking treatable traits and biomarker signatures to candidate targeted therapies. A pragmatic roadmap is to (1) define the dominant treatable trait(s)—e.g., hyperinflammation, immunoparalysis, endothelial barrier failure, coagulopathy/immunothrombosis, or catecholamine-resistant vasoplegia—using clinically feasible markers; (2) apply enrichment with biomarkers and/or physiological tests to identify patients most likely to respond; and (3) reassess response dynamically to account for the strong time-dependence of sepsis biology. In this context, Table 1 summarizes candidate biomarker–therapy matches that can guide trial design and, where evidence supports, clinical decision-making.

For immunomodulation, prior studies suggest that a "one-size-fits-all" approach may dilute treatment effects, whereas biomarker-guided enrichment can reveal signals of benefit in selected subgroups. For example, corticosteroid responsiveness appears to vary across immune endotypes and biomarker signatures (e.g., transcriptomic endotypes and theranostic cytokine ratios), supporting prospective biomarker-guided strategies to identify steroid-sensitive versus steroid-resistant patients.

Similarly, anticoagulant/endothelial-targeted strategies such as activated protein C and related approaches have shown heterogeneous effects across populations; subgroup analyses and mechanistic reasoning support focusing future trials on patients with marked protein C pathway dysfunction and/or sepsis-associated coagulopathy phenotypes, while carefully balancing bleeding risk.

Determining individualized hemodynamic targets should also follow a precision paradigm. While an initial MAP target of ~ 65 mmHg is reasonable for many patients, subsequent targets should be individualized based on comorbidities (e.g., chronic hypertension), organ-specific vulnerability, and real-time perfusion assessment. A practical strategy is a short MAP challenge, evaluating changes in perfusion surrogates (urine output, mental status, skin perfusion/capillary refill time) during a transient MAP increase; if perfusion improves, the higher MAP can be adopted, whereas lack of benefit or intolerance supports returning to the lower target. This approach integrates guideline-based care with patient-specific physiology and limits iatrogenic vasopressor exposure.

Conclusions

Sepsis and septic shock are increasingly recognized as heterogeneous syndromes driven by distinct immune, endothelial, and metabolic trajectories. This recognition challenges uniform treatment paradigms and supports a shift toward biologically informed, phenotype-aligned adjunctive strategies layered upon standard care. Future progress will depend on prospective, biomarker-guided trials capable of translating mechanistic insight into reproducible improvements in patient outcomes.

Abbreviations

aPTT	Activated partial thromboplastin time
ANG I/II	Angiotensin I/II ratio
ARDS	Acute respiratory distress syndrome
Ang II	Angiotensin II
BioADM	Bioactive adrenomedullin
CD45/CD14	Monocyte surface markers used for HLA-DR quantification
CRH	Catecholamine-resistant hypotension
CXCL9	C-X-C motif chemokine ligand 9
DAMPs	Damage-associated molecular patterns
DIC	Disseminated intravascular coagulation
EAA	Endotoxin activity assay
ECMO	Extracorporeal membrane oxygenation
ESS	Endotoxic septic shock
FDPs	Fibrin degradation products
HA	Hemoadsorption
HLA-DR	Human leukocyte antigen-DR
HUS	Hemolytic uremic syndrome
ICAM-1	Intercellular adhesion molecule-1
ICU	Intensive care unit
IDS	Interferon-γ-driven sepsis
IFN-γ	Interferon gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-10	Interleukin-10
IVIG	Intravenous immunoglobulin
MAP	Mean arterial pressure
MALS	Macrophage activation-like syndrome
MFI	Microvascular flow index
MODS	Multiple organ dysfunction score
MPO–DNA	Myeloperoxidase–DNA complexes
MR-proADM	Mid-regional proadrenomedullin
NE	Norepinephrine
NED	Norepinephrine equivalent dose
NETs	Neutrophil extracellular traps
PAMPs	Pathogen-associated molecular patterns
PBR	Perfused boundary region
PMX	Polymyxin B
PMX-HA	Polymyxin B hemoadsorption
PT	Prothrombin time
RAAS	Renin–angiotensin–aldosterone system
RCT	Randomized controlled trial
rhIFN-γ	Recombinant human interferon gamma
RRT	Renal replacement therapy
rTM	Recombinant thrombomodulin
S1P	Sphingosine-1-phosphate
SHINE	Shock-induced endotheliopathy
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
sTM	Soluble thrombomodulin
$SvcO_2$	Central venous oxygen saturation
TAMOF	Thrombocytopenia-associated multiple organ failure
TAT complexes	Thrombin–antithrombin complexes
TIGRIS	Therapeutic investigation of glycoregulation in sepsis
TMA	Thrombotic microangiopathy
TPE	Therapeutic plasma exchange
TREM-1	Triggering receptor expressed on myeloid cells-1
TTP	Thrombotic thrombocytopenic purpura
VCAM-1	Vascular cell adhesion molecule-1
VE-cadherin	Vascular endothelial cadherin
VIS	Vasoactive-inotropic score
VWF	Von Willebrand factor

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