

REVIEW

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# Targeting the host response in sepsis: current approaches and future evidence

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## Abstract

Sepsis, a dysregulated host response to infection characterized by organ failure, is one of the leading causes of death worldwide. Disbalances of the immune response play an important role in its pathophysiology. Patients may develop simultaneously or concomitantly states of systemic or local hyperinflammation and immunosuppression. Although a variety of effective immunomodulatory treatments are generally available, attempts to inhibit or stimulate the immune system in sepsis have failed so far to improve patients' outcome. The underlying reason is likely multi-faceted including failure to identify responders to a specific immune intervention and the complex pathophysiology of organ dysfunction that is not exclusively caused by immunopathology but also includes dysfunction of the coagulation system, parenchymal organs, and the endothelium. Increasing evidence suggests that stratification of the heterogeneous population of septic patients with consideration of their host response might lead to treatments that are more effective. The purpose of this review is to provide an overview of current studies aimed at optimizing the many facets of host response and to discuss future perspectives for precision medicine approaches in sepsis.

**Keywords** Septic shock, Clinical studies, Disease tolerance, Immunomodulation, Immunotherapy, Biomarkers, Precision medicine, Immunosuppression, Personalized medicine

## Introduction

Sepsis remains a leading cause of death worldwide, despite our advances in critical care medicine [1]. First immunotherapeutic approaches that aimed at controlling the early hyperinflammatory phase were not successful in clinical trials. Subsequent deeper insight into the pathophysiology revealed that systemic hyperinflammation,

characterized by high levels of circulating pro-inflammatory markers such as cytokines or ferritin and the concomitant presence of organ dysfunction, does not necessarily characterize all sepsis patients. Instead, some patients are found to be rather systemically immunosuppressed. The common denominator infection-associated organ dysfunction can also occur independently of these two extremes and local immune responses may vary from the blood compartment (Fig. 1) [2, 3]. As a consequence, sepsis was redefined as a dysregulated host response to infection [4]. In medicine, the field of immunotherapeutics for other disease has rapidly evolved, leading to countless effective treatment strategies, e.g., to control tumor growth or limit autoimmunity [5]. As an analogy, the development of specific adapted therapies targeting the dysregulated host response in sepsis may improve the outcome of some of our patients. Potentially, it is the heterogeneity of the syndrome and the associated difficulties in matching the right patient to a given treatment that resulted in little success in the clinical

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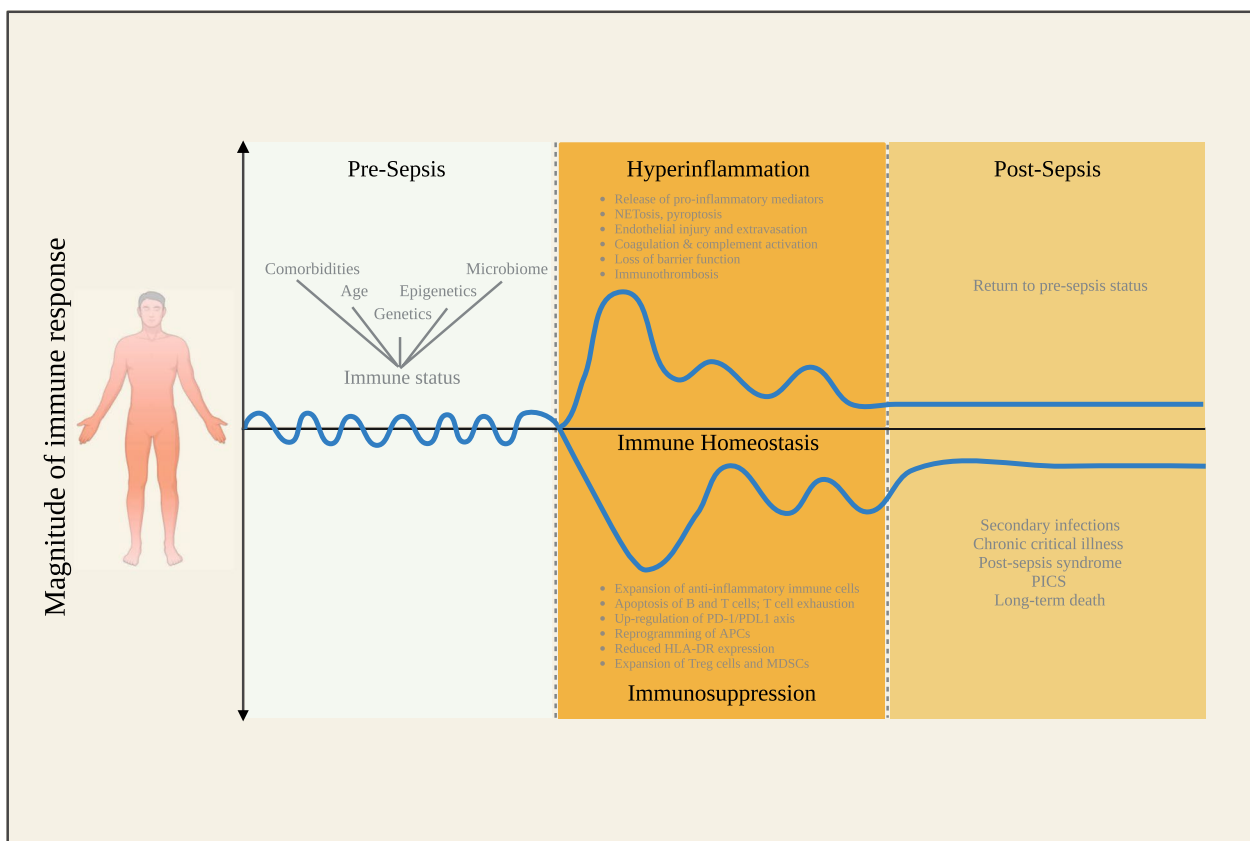
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**Fig. 1** Model of sepsis-induced immune responses. This extended model of sepsis-induced immune responses describes the host inflammatory response before, during, and after sepsis. Infection modifies the innate and adaptive immune response for sustained periods of time, even long after clinical recovery. The immune response in sepsis is highly personalized and contingent upon the patient’s immune status when infection occurs. This status is influenced by various factors including age, comorbidities, environmental elements, and the microbiome. Moreover, each patient exhibits a highly intricate combination of genetic variations and epigenetic alterations, rendering their immune system a virtually unique selection of genes responsible for cytokines and mediators that regulate immune responses. Excessive inflammation is triggered by the release of pro-inflammatory mediators by various cell types upon detecting pathogen-associated molecular patterns (PAMPs). Simultaneously, the activation of the complement system, the vascular endothelium, and the coagulation system results in microcirculatory disturbances. These processes are exacerbated by the release of damage-associated molecular patterns (DAMPs) as a consequence of tissue damage, the discharge of neutrophil extracellular traps (NETosis), and inflammatory cell death (pyroptosis). Immune suppression can develop at various time points and is characterized by the secretion of anti-inflammatory cytokines, the apoptosis of T cells, B cells, and dendritic cells, T cell exhaustion, and the proliferation of anti-inflammatory immune cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Immune suppression is further intensified by decreased expression of human leukocyte antigen–antigen D related (HLA-DR) and heightened expression of programmed cell death 1 (PD-1) and its corresponding ligand (PD-L1). Post sepsis, the immune response can return to pre-sepsis status; however, many sepsis survivors later succumb to secondary infections, chronic critical illness, post-sepsis syndrome, and post-intensive care syndrome (PICS), severely impacting quality of life. A persistent sepsis-induced immune dysfunction can eventually lead to long-term death

setting so far [6]. Here, we provide an overview of current approaches to target the many facets of the host response and discuss future perspectives in the field of precision immunotherapy.

**Targeting hyperinflammation**

**Selective immunomodulators**

**Tumor necrosis factor**

Tumor necrosis factor (TNF) plays a crucial role in the systemic inflammatory response, and biologics that

neutralize TNF are among the most successful drugs for the treatment of various chronic inflammatory diseases [7]. However, initial clinical trials targeting TNF in sepsis patients yielded disappointing results [8–12]. A meta-analysis of 17 randomized controlled trials (RCTs) involving more than 8000 septic patients treated with anti-TNF showed a small but significant reduction in 28-day all-cause mortality [13]. Interestingly, in a study of 2634 sepsis patients, treatment with the anti-TNF antibody (Ab) afelimomab resulted in a modest but

significant reduction in 28-day mortality if serum IL-6 levels were > 1000 pg/mL, while patients with lower IL-6 levels did not benefit from treatment [14]. This suggests that a specific subset of patients identified by biomarkers may benefit from anti-TNF therapy.

#### **Interleukin-1 receptor**

IL-1 signaling is mediated by the two distinct ligands IL-1 $\alpha$  and IL-1 $\beta$ , both of which act on the IL-1 receptor (IL-1R) to trigger inflammation [15]. While IL-1  $\beta$  is mainly released by activated immune cells, IL-1 $\alpha$  is a nearly ubiquitous alarmin released by injured tissue. There has long been interest in the deleterious role of IL-1R signaling in sepsis, but RCTs did not show a significant prolongation of survival [16, 17]. Interestingly, a retrospective analysis of 529 sepsis patients found that anakinra significantly reduced mortality when baseline plasma IL-1RA levels were above 2071 pg/mL [18]. In a further re-analysis of a multicenter (m)RCT, 763 patients were re-grouped according to the presence of features of macrophage activation syndrome (MAS) in the form of disseminated intravascular coagulation (DIC) and hepatobiliary dysfunction (HBD) [19]. In this study, anakinra was associated with a significant improvement in survival of patients with sepsis and concomitant HBD/DIC. Recently, the mRCT SAVE-MORE has stratified coronavirus disease 2019 (COVID-19) patients with mild to severe pneumonia according to a soluble urokinase-type plasminogen activator receptor (suPAR) level  $\geq 6$  ng/mL and tested anakinra compared to standard of care (SoC) [20]. Anakinra treatment provided higher odds for clinical improvement and lowered the 28-day mortality from 6.9 to 3.2%. SuPAR and MAS features illustrate the biological and clinical consequences of hyperinflammation such as coagulopathy and tissue damage [21]. The results of the above studies therefore suggest that these classes of biomarkers may enable more targeted anakinra treatment in sepsis.

#### **Interleukin-6**

Interleukin-6 (IL-6) is another important cytokine involved in the innate immune response in sepsis [6]. IL-6 inhibitors are the approved treatment for the hyperinflammatory state of CAR-T cell-induced cytokine release syndrome [22]. Recently, IL-6 inhibition has been studied in the COVID-19 pandemic with conflicting results. However, two studies pooling data from previous trials involving more than 10,000 critically ill COVID-19 patients show that IL-6 inhibitor administration was associated with lower 28-day all-cause mortality [23, 24]. Although it is currently unclear whether IL-6 inhibition has similar benefits in other cases of sepsis, a recent Mendelian randomization analysis suggests that

IL-6 receptor blockade was associated with lower mortality in 11,643 patients of the UK Biobank cohort with non-COVID-19 sepsis [25]. Overall, these data suggest that a mRCT of IL-6 inhibition in sepsis, ideally as part of a predictive enrichment approach, should at least be considered.

#### **Complement inhibition (anti-C5a)**

The complement system is a key regulator of immunity that bridges the innate to the adaptive response, and that contributes to opsonization and lysis of invading pathogens. The complement cascade can be activated via three pathways by invading pathogens and also via, e.g., tissue damage and the associated release of endogenous danger molecules (DAMPs) [26]. Normally, the complement system plays a protective role but can also directly contribute to a hyperinflammatory state triggering the development of complications like multiple-organ failure. Experimental studies have linked hyperinflammation and endothelial barrier breakdown with complement activation and some trials have shown benefits using inhibitory strategies in non-human primates and pigs with regard to the incidence of organ failure, coagulopathy, and even survival [27–30]. A phase IIa mRCT (SCIENS-trial) investigated complement inhibition in sepsis using three different doses of a monoclonal anti-C5a antibody (vilobelimab). This pharmacodynamics/-kinetic study demonstrated efficient inhibition of C5a and some secondary efficacy endpoints. The authors reported that patients receiving higher dosages of vilobelimab had more intensive care unit (ICU)-, vasopressor-, and ventilator-free days [31] (Table 1).

#### **Non-selective immunomodulators**

##### **Corticosteroids**

Glucocorticoids have potent anti-inflammatory properties such as inhibition of innate immune response and endothelial activation [32]. Clinical trials of glucocorticoids in sepsis yielded controversial results, with some showing improved outcomes and others reporting no or even adverse effects [33]. Therefore, current guidelines contain only a weak recommendation for hydrocortisone in septic shock [34]. Recently, however, a clear indication for dexamethasone in severe COVID-19 has been established, shedding new light on the efficacy of glucocorticoids in a homogenous population of critical ill patients [35–37]. In addition, recent data, including the CAPE-COD trial, showed that patients with severe community-acquired pneumonia who received hydrocortisone had a lower mortality rate [38, 39]. These promising data from specific patient populations may also lead to a renaissance of glucocorticoid therapy in the context of subgrouping sepsis patients [37].

**Table 1** Recent clinical studies that target hyperinflammation in sepsis\*

Anti-inflammatory agent	Mechanism of action	Study population	Primary outcome	Results	Author, year of publication or NCT number
Vitamin C	Inhibition of NF- $\kappa$ B activation and HMGB1 release, enhancement of chemotaxis and phagocytosis	n = 872, proven or suspected infection (ICU stay < 24 h) and vasopressor therapy n = 167, sepsis and ARDS (< 24 h)	Composite of death or persistent organ dysfunction on day 28 Modified SOFA score at 96 h, CRP and thrombomodulin levels at 168 h	Higher risk of death or persistent organ dysfunction on day 28 No significant difference in primary endpoints	Lamontagne et al. 2022 [42] Fowler et al. 2019 [40]
Hydrocortisone, vitamin C, thiamine	Pleiotropic immunomodulatory effects (e.g., inhibition of NF- $\kappa$ B, AP-1, endothelial and neutrophil activation)	n = 216, early septic shock (< 24 h)	Time alive and free of vasopressors on day 7	No significant difference in primary endpoints	Fujii et al. 2020 [41]
Clarithromycin	Wide-ranging immunomodulatory effects (e.g., inhibition of TLR expression and signaling, inhibition of pro-inflammatory cytokine, chemokine and DAMPs release)	n = 110, sepsis, ARDS and multiple-organ dysfunction	28-day mortality	No significant difference, lower incidence of sepsis recurrence, significant increase in monocyte HLA-DR expression; expansion of non-classical monocytes; and upregulation of genes involved in cholesterol homeostasis	Karakike et al. 2022 [51]
Vilobelimab	Novel monoclonal anti-C5a antibody	n = 72, sepsis or septic shock	pharmacodynamics, pharmacokinetics, safety	Dose-dependent neutralization of C5a, higher ICU- and ventilator-free days	Bauer et al. 2021 [31]
Thrombomodulin (ART-123)	Binding of thrombin, activation of protein C, inhibition of DAMPs associated inflammation and organ injury	n = 800, sepsis-associated coagulopathy	28-day mortality	No significant difference	Vincent et al. 2019 [58]
Adreicuzumab (HAM8101)	Non-neutralizing adrenomedullin antibody	n = 301, septic shock	Safety (90-day mortality, adverse events), tolerability	No significant difference in 90-day mortality and adverse events, well tolerated	Laterre et al. 2021 [63]
Cytokine adsorption	Adsorption of PAMPs, DAMPs and cytokines	n = 2611, septic shock, cardiac arrest, cardiopulmonary bypass surgery, severe illness n = 96, septic shock	Longest reported mortality	No significant difference	Becker et al. 2023 [67]
Coupled plasma filtration and adsorption	Adsorption of pro-inflammatory and anti-inflammatory mediators	n = 115, septic shock	Mortality at hospital discharge	No difference in IL-6 and vasopressor requirements, increased mortality hazard ratio Significantly higher mortality, trial stopped for futility	Wendel Garcia et al. 2021 [65] Garbero et al. 2021 [66]

**Table 1** (continued)

Anti-inflammatory agent	Mechanism of action	Study population	Primary outcome	Results	Author, year of publication or NCT number
Therapeutic plasma exchange (TPE)	Elimination of pro-inflammatory and replacement of protective molecules	n = 40, early septic shock (< 24 h)	Early hemodynamic improvement	Significant hemodynamic improvement over first 24 h, higher baseline lactate levels were predictive for more efficient hemodynamic improvement; significant reduction of procalcitonin (PCT), soluble receptor of tyrosine kinase with immunoglobulin-like and EGF-like domains (sTie-2), von Willebrand factor antigen (vWF:Ag); significant repletion of antithrombin-III, ADAMTS13, protein C	Stahl et al. 2022 [68] David et al. 2021 [70]
		n = 20, early septic shock (< 24 h)	Levels of endothelial glycoalyx degradation products (heparan sulfate (HS), heparinase (Hpa)-1 and -2)	HS levels significantly reduced, significantly normalized Hpa-2/Hpa-1 ratio, attenuation of eGc damage ex vivo with serum from TPE group	Stahl et al. 2021 [72]
		n = 80, septic shock and evidence of multiple-organ failure	28-day mortality	Significantly reduced 28-day mortality	Keith et al. 2020 [69]
		n = 274, early septic shock (< 24 h)	28-day mortality	Not yet recruiting	NCT05726825 (EXCHANGE-2)
		n = 80, early septic shock (< 24 h)	Feasibility of a large, multicenter trial of TPE in patients with septic shock	Not yet recruiting	NCT05093075 (PLEXSIS)

\*A summary of clinical studies over last past 5 years

### **Vitamin C**

Vitamin C is an antioxidant with pleiotropic anti-inflammatory activity that is depleted in response to oxidative stress, which is one reason to investigate the effect of vitamin C, either alone or in random combinations with hydrocortisone and thiamine [20]. While initial studies suggested improved outcomes in sepsis [6], further studies could not confirm a beneficial effect. The CITRIS-ALI RCT showed that vitamin C did not significantly improve organ dysfunction scores or inflammatory markers in patients with sepsis and ARDS [40]. Similarly, the VITAMINS trial, which examined the use of vitamin C in septic shock, found no significant improvement in survival without vasopressor administration for 7 days [41]. The LOVIT trial, an RCT including patients with septic shock, found that vitamin C therapy increased the risk of a composite end point—death or persistent organ dysfunction at day 28 [42]. Yet, recent meta-analyses found an improvement in delta—sequential organ failure assessment (delta-SOFA) score and a reduction in the duration of vasopressor use, whereas short-term mortality was not affected [43, 44]. Because the role of vitamin C in sepsis remains uncertain, it should only be used in the context of RCTs. Such studies are underway and may provide more insight into optimal dosing and treatment duration, as well as the patient population that will benefit most from vitamin C therapy (Table 1).

### **Antibiotics with anti-inflammatory properties**

In addition to their antibacterial action, tetracyclines and macrolides in particular exert pleiotropic immunomodulatory effects that may be able to limit the hyperinflammatory response in patients with sepsis. In experimental sepsis, tetracyclines limit the inflammation-caspase-1 pathway and promote disease tolerance to infection [45–48]. In a RCT of 231 dengue fever patients, treatment with doxycycline was associated with lower mortality, which correlated positively with lower levels of pro-inflammatory cytokines [49].

Recent studies using macrolides in acute respiratory distress syndrome (ARDS) patients have shown a survival benefit and shorter time to successful discontinuation of mechanical ventilation [50]. An mRCT found no effect of clarithromycin on mortality in sepsis patients with respiratory and multiple-organ dysfunction [51] (Table 1). However, clarithromycin was associated with a lower recurrence of sepsis, a significant increase in monocyte human leukocyte antigen-DR isotype (HLA-DR) expression, and an expansion of monocytes, suggesting a possible role for macrolides in immune recovery [51].

### **(Activated) protein C and thrombomodulin**

A controlled interaction between the endothelium, the immune, and the coagulation system is a conserved and physiologically required process. Nevertheless, in dysregulated settings it can spark systemic microvascular clotting, often referred to as immunothrombosis [52]. In sepsis, these phenomena can contribute to disseminated intravascular coagulation (DIC), thus further damaging tissues and organs opening potential avenues for therapeutic targets [6]. Yet, anticoagulants like heparin and P2Y12 inhibitors show only variable benefits accompanied by high bleeding risks [53].

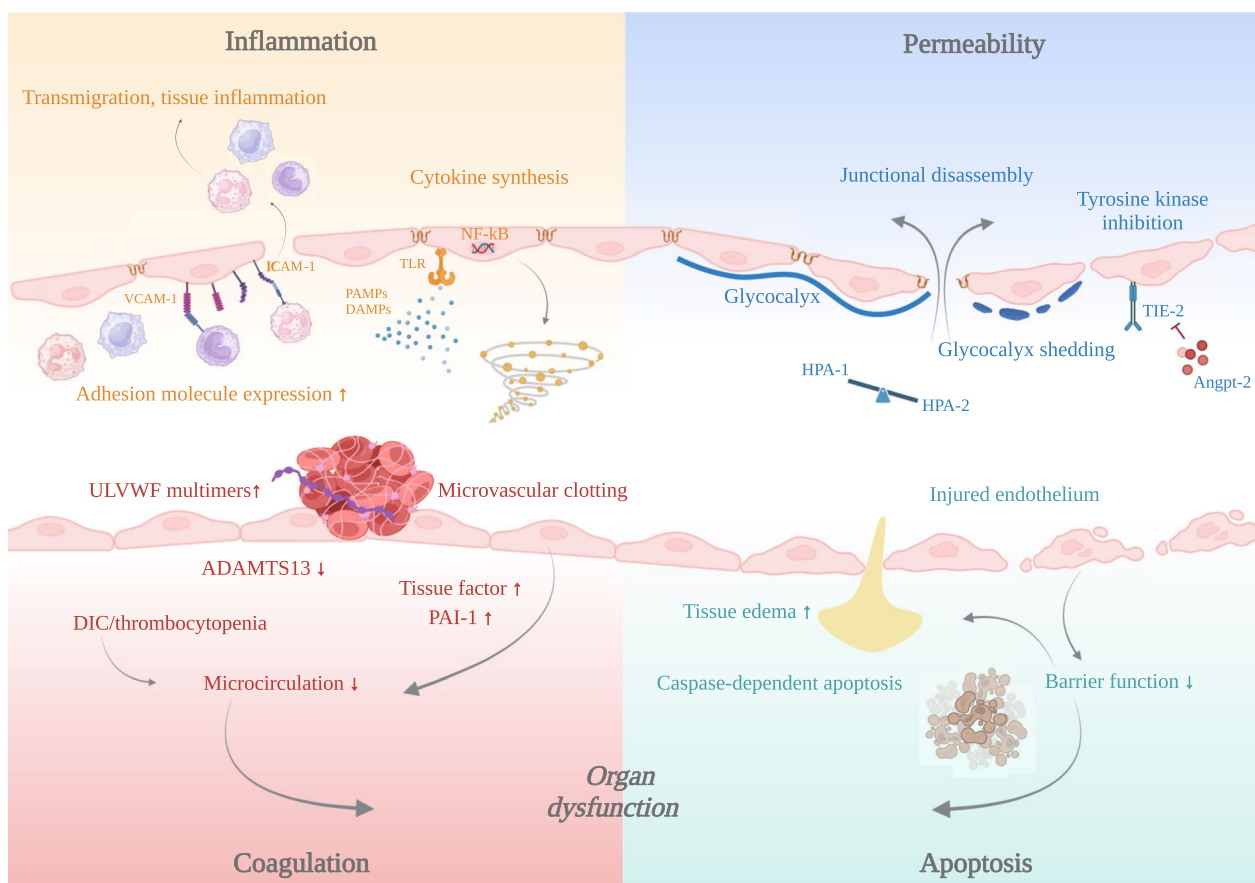
Activated protein C (APC) is a naturally occurring anticoagulant that when given as the recombinant form (Xigris [drotrecogin alfa]) inhibits and reduces the expression of tissue factor; it was the first biologic specific agent to be approved for the treatment of severe sepsis and septic shock based on the PROWESS trial that showed a reduction in 28-day mortality [54]. These results could not be replicated in subsequent trials, ultimately leading to the withdrawal of APC in 2011 from the market [55, 56].

More recently, the focus has been on recombinant thrombomodulin (ART-123), which promotes protein C activation and has additional anti-inflammatory properties [57]. However, treatment with ART-123 did not improve survival in three RCTs [58–60]. A recent meta-analysis of these trials found that ART-123 reduced 28-day mortality only in a subgroup of patients with evidence of sepsis-associated coagulopathy [61].

### **Bioactive adrenomedullin**

The response of the endothelium to inflammatory stimuli is per se an evolutionary-derived protective mechanism to control infections. Any of its physiological function can be affected [62]. As a net result, the quiescent “healthy” endothelium changes toward a procoagulant, pro-adhesive, pro-inflammatory, and hyper-permeable phenotype together with a macrovascular vasoplegia (Fig. 2). All these alterations are part of a complex physiological response to an infection, but the simultaneous and systemic occurrence can have fatal consequences.

Among all endothelial alterations, systemic capillary leakage is a particularly relevant player in the pathophysiology of septic multiple-organ failure. The molecular mechanisms involved in the formation of gaps between adjacent endothelial cells (EC) are tightly controlled by a variety of proteins that might serve as therapeutic targets. As an example, bioactive adrenomedullin (bioADM) is a small molecule with differential functions dependent on both its localization (intra- or extravascular) and the target cell (EC or vascular smooth muscle cells (VSMC)). Intravascular bioADM has protective anti-permeability



**Fig. 2** Vascular endothelial dysfunction in the pathogenesis of septic organ injury. The vascular endothelium plays a crucial role in inflammation, immunothrombosis, and vascular barrier integrity. During sepsis, the activation of a highly complex inflammatory cascade by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) triggers the production of pro-inflammatory, proapoptotic, and procoagulant mediators by both immune cells and vascular endothelial cells (ECs). Toll-like receptor (TLR) signaling causes nuclear translocation of transcription factor NF-κb, leading to a deleterious cytokine release syndrome. The luminal surface of the vascular endothelium is lined by the endothelial glycocalyx (eGC), a gel-like carbohydrate-rich structure. In sepsis, heparanase-1 (HPA-1) activity is upregulated inducing degradation of the eGC. Glycocalyx shedding exposes embedded adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) which both enable leukocyte rolling, adhesion, and transmigration. Loss of the eGC, junctional disassembly, and EC apoptosis result in capillary barrier dysfunction, increased permeability, and interstitial tissue edema. Besides amplifying the inflammatory host response, ECs also promote a prothrombotic state leading to microvascular clotting and frequently disseminated intravascular coagulation (DIC). A lack of cleavage of von Willebrand factor (VWF) due to reduced levels of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) contributes to the accumulation of ultra-large VWF (ULVWF) multimers facilitating platelet adhesion to injured endothelium. The upregulation of tissue factor which initiates extrinsic coagulation and plasminogen activator inhibitor 1 (PAI-1), the main inhibitor of fibrinolysis, further augments the process of sepsis-induced immunothrombosis

effects. However, if it is localized outside the vasculature this protection is lost triggering increased permeability. Simultaneously, extravascular bioADM promotes VSMC relaxation thereby aggravating hypotension and shock. Adreuzumab is a non-functional antibody to bioADM. Ligation increases its size thereby losing the capability to migrate to the interstitial space but maintaining its beneficial barrier protective effects. A recent feasibility RCT (AdrenOSS-2) confirmed not only safety of the substance but also some promising signals with regard to secondary efficacy endpoints [63, 64] (Table 1).

**Extracorporeal blood purification**

The field of extracorporeal strategies to modulate the host response has been growing over the last decade. Focusing on adsorptive technologies, it has been postulated that the removal of pro-inflammatory mediators during early and severe septic shock might be beneficial. Numerous uncontrolled reports support this notion, but evidence from controlled trial is sparse. Besides a few negative trials and trials that even indicated potential harm [65, 66], a 2023 meta-analysis including RCTs and propensity matched analysis did not show any benefit

but also no harm with regard to mortality [67]. Therapeutic plasma exchange (TPE) has shown some promising results in removing injurious and replacing protective but consumed proteins thereby rebalancing hemostasis in septic shock [68–70]. This approach does not only address the immune response but also targets the well established link to coagulopathy and vascular barrier breakdown. Two examples are the von Willebrand (VWF) system and the endothelial glycocalyx (eGc).

First, to avoid microangiopathic obstruction of the microcirculation, systemically released VWF is enzymatically cleaved by a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). During septic shock, this process consumes ADAMTS13 aggravating microvascular clotting and consequently organ malperfusion. Second, the eGc is a gel-like layer that mostly consists of sugars such as proteoglycans and glycosaminoglycans that regulates inflammation, permeability, and coagulation. In sepsis, a distinct regulation of counteracting enzymes (i.e., heparanases) can lead to massive degradation of the eGc [71].

TPE can rebalance these disequilibria by removing VWF and heparanase-1 and by replacing protective ADAMTS13 and heparanase-2 [72]. Two meta-analysis even suggests a potential survival benefit triggering large mRCTs in both Europe (EXCHANGE-2, NCT05726825) and Canada (PLEXSIS, NCT05093075) that are about to start soon [73, 74] (Table 1).

## Immune augmentation strategies

### Immunostimulatory cytokines and growth factors

#### *Granulocyte–macrophage colony-stimulating factor*

Granulocyte–macrophage colony-stimulating factor (GM-CSF), a hematopoietic growth factor, restores HLA-DR expression on monocytes [75]. In sepsis patients with decreased monocytic HLA-DR, an mRCT demonstrated GM-CSF reduced the need for mechanical ventilation and increased TLR2/4-induced cytokines [76]. A meta-analysis found improved infection resolution, but no associated mortality benefit [77]. In a recent mRCT assessing HLA-DR-guided GM-CSF therapy's impact on ICU-acquired infection in immunosuppressed septic patients, no differences were observed in ICU-acquired infection or 28-day mortality [78]. The study ended prematurely after enrolling 98 of 166 planned patients, limiting conclusive findings. Comprehensive immunophenotyping beyond monocyte HLA-DR may be needed for better predictive enrichment. In light of this approach, a recent RCT in children with sepsis defined immunoparalysis treated with GM-CSF as an LPS-induced TNF production capacity <200 pg/mL (NCT05266001) (Table 2).

### *Interferon gamma*

Interferon gamma (IFN $\gamma$ ) activates macrophages, NK cells, and neutrophils, bolstering immune responses against pathogens [79]. In septic patients, low IFN $\gamma$ -secretion is linked to secondary infection or death, while IFN $\gamma$ -treatment increases HLA-DR expression and production of pro-inflammatory cytokines [80–83]. An mRCT on IFN $\gamma$  for sepsis-related immune paralysis ended early due to slow enrollment (<30% CD14 monocytes with HLA-DR) [84]. Another mRCT uses a cutoff of <5000 HLA-DR receptors per CD14 monocyte for septic immunosuppression treatment [85] (Table 2). However, high IFN $\gamma$  levels in early sepsis are associated with secondary candida infection, suggesting its role as an immunosuppressive mediator [86]. These negative effects might contribute to the early termination of another RCT to prevent hospital-acquired pneumonia in a heterogeneous group of patients, highlighting the need to stratify septic patients for IFN $\gamma$  use in an immunosuppressive subphenotype [87].

### *Thymosin alpha 1*

Thymosin alpha 1 (TA1) is a peptide synthesized primarily in the thymus gland and has long been known to modulate, enhance, and restore immune function. TA1 activates TLR2 and -9 in myeloid and dendritic cells, promoting adaptive responses and CD4+/CD8+ T cell maturation [88]. An mRCT with 367 septic patients showed increased monocyte HLA-DR expression and a trend toward improved survival ( $p=0.06$ ) in patients receiving TA1 [89]. A meta-analysis of 12 trials revealed lower sepsis mortality, but caution is needed due to individual study quality and size [90]. A large mRCT involving 1106 patients was recently completed. Its results may provide further insight into the therapeutic effect of TA1 in sepsis (NCT02867267 and NCT04901104, Table 2).

### Immunoglobulins

Intravenous immunoglobulins (IVIg) are used to neutralize microbes, reduce apoptosis of immune cells, limit inflammation, and mediate phagocytosis by macrophages. In septic patients, studies have demonstrated correlations between survival probability and concentrations of IgG, IgM, and IgA [91, 92]. RCTs on IVIg treatment in sepsis showed conflicting outcomes. Meta-analyses indicated reduced mortality with IVIg and IgM-enriched IVIg (IVIgM) [93, 94]. However, due to study quality variations, dosing differences, and control measures, evidence quality is low. Current guidelines advise against IVIg use in sepsis [34]. A large RCT is currently underway to investigate the effect of IVIgM therapy in sepsis patients (NCT03334006) (Table 2). This trial is monitoring several biomarkers, including Igs, cytokines,



**Table 2** Recent clinical studies that target immunosuppression in sepsis\*

Immune augmentation agent	Mechanism of action	Study population	Primary outcome	Results	Author, year of publication or NCT number
GM-CSF	Increased monocyte HLA-DR expression Increased monocyte production of TLR2/4-induced cytokines	n = 98, septic shock	Difference in the number of patients presenting $\geq$ 1 ICU-acquired infection at day 28 or ICU discharge	No significant difference; terminated due to insufficient recruitment	Vacheron et al. 2023 [78]
IFN $\gamma$	Primary activator of macrophages, neutrophils, and natural killer cells	n = 400, children with sepsis-induced multiple-organ dysfunction syndrome (MODS)	Cumulative 28-day Pediatric Logistic Organ Dysfunction (PELOD)-2 score	Recruiting	NCT05266001 (GRACE2)
		n = 273, sepsis and septic shock n = 280, sepsis (< 72 h)	28-day mortality Comparative decrease of the mean total Sequential Organ Failure Assessment (SOFA) score by at least 1.4 points by day 9 from randomization	No significant difference Recruiting	Leventogiannis et al. 2022 [84] Kotsaki et al. 2022 NCT04990232 (ImmunoSep) [85]
Thymosin alpha	Stimulates endogenous IFN $\gamma$ secretion and regulates T cell subsets	n = 1106, sepsis sepsis patients discharged after completing TESTS trial	28-day mortality 3-year mortality	Pending Pending	NCT02867267 NCT04901104
Immunoglobulins (IgM-enriched)	Enhancement of pathogen recognition and clearance, scavenging of toxins and complement, neutralization of inflammatory cytokines	n = 200, sepsis or septic shock	Improvement of the mean multiple-organ failure score on day 7	Pending	NCT03334006
Mesenchymal stem cells (MSC)	Augmentation of bacterial clearance, limitation of apoptosis, injury repair enhancement	n = 9, septic shock	Safety, tolerability	Well tolerated, no infusion-associated, and serious adverse events	McIntyre et al. 2018 [101]
		n = 15, septic shock	Safety, tolerability	Well tolerated, no infusion-associated, and serious adverse events	He et al. 2018 [102]
		n = 114, sepsis and septic shock	Reduction in days on mechanical ventilation, or renal replacement therapy, or vasopressors; safety and tolerability Sofa score on day 7	Pending	NCT03369275 (CISS2)
		n = 66, septic shock ( $\geq$ 2 organ failures other than hemodynamic) n = 21, septic shock	Safety, tolerability	Pending	NCT02883803 (CHOCMSC) NCT04961658 (AMETHYST)

**Table 2** (continued)

Immune augmentation agent	Mechanism of action	Study population	Primary outcome	Results	Author, year of publication or NCT number
nivolumab	Anti-programmed cell death (PD)-1 monoclonal antibody	n = 13; sepsis	Safety, tolerability, pharmacokinetics	Safe, well tolerated, increase in lymphocyte count and mHLA-DR expression	Watanabe et al. 2020 [114]
		n = 31, sepsis diagnosed $\geq$ 24 h before treatment, $\geq$ 1 organ dysfunction, and absolute lymphocyte count $\leq$ $1.1 \times 10^3$ cells/ $\mu$ L	Safety, tolerability and pharmacokinetics over 90d	Safe, no cytokine release syndrome	Hotchkiss et al. 2019 [115]

\*A summary of clinical studies over last past 5 years

and cellular HLA-DR expression, to determine which subgroup of patients (those with hyperinflammation or immunosuppression) may benefit from IVIgM treatment.

### Mesenchymal stem cells

Multipotent mesenchymal stem cells (MSCs) hold promise for sepsis immunotherapy due to their immunomodulatory, antimicrobial, regenerative, and anti-apoptotic properties. In preclinical models, MSC application rebalances inflammation by suppressing pro-inflammatory cytokines and enhancing anti-inflammatory mediators [95, 96]. MSCs restore organ structure and function, including kidneys and liver, and boost phagocytic activity of monocytes against gram-negative sepsis [97, 98]. Meta-analyses indicate lower sepsis mortality with MSC therapy in animal models [99, 100]. Phase I trials on septic shock patients and COVID-19 ARDS cases showed MSCs' safety and limited adverse events [101–103]. Several ongoing phase I and II sepsis trials (NCT03369275, NCT02883803, NCT04961658) will provide more insights into MSC therapy's safety and efficacy (Table 2).

### Immune checkpoint inhibitors

Immune checkpoint receptors are important immune modulators that are critical for self-tolerance and regulation of ongoing immune responses. Several checkpoint receptors including programmed cell death protein 1 (PD-1), B and T lymphocyte attenuator (BTLA), and lymphocyte activation gene 3 (LAG-3), along with their respective ligands such as PD-L1, are upregulated on leukocytes during sepsis [104]. PD-1/PD-L1 upregulation on CD4+ lymphocytes and plasmacytoid dendritic cells is seen in sepsis-related immunosuppression [105]. Increased BTLA and PD-1 expression on CD4+ lymphocytes links to secondary infections, prolonged ICU stays, and higher mortality [106, 107]. Targeting PD-1/PD-L1 in preclinical studies counters apoptosis, restores cell function, and improves survival [108–110]. Ex vivo inhibition of the PD-1/PD-L1 pathway reduced apoptosis, improved immune cell function, and increased cytokine production in leukocytes from septic patients [111, 112]. In a case study of an immunocompromised patient with refractory fungal sepsis, it was observed that combined administration of anti-PD-1 antibody and IFN $\gamma$  resulted in an increase in lymphocyte count and enhanced expression of monocytic HLA-DR [113]. The PD-1 inhibitor nivolumab was shown to be well tolerated in two-phase I trials conducted in immunocompromised patients with sepsis [114, 115] (Table 2). In these two trials, nivolumab also appeared to improve immune function by increasing monocytic HLA-DR expression and lymphocyte counts.

### Personalized immunotherapy

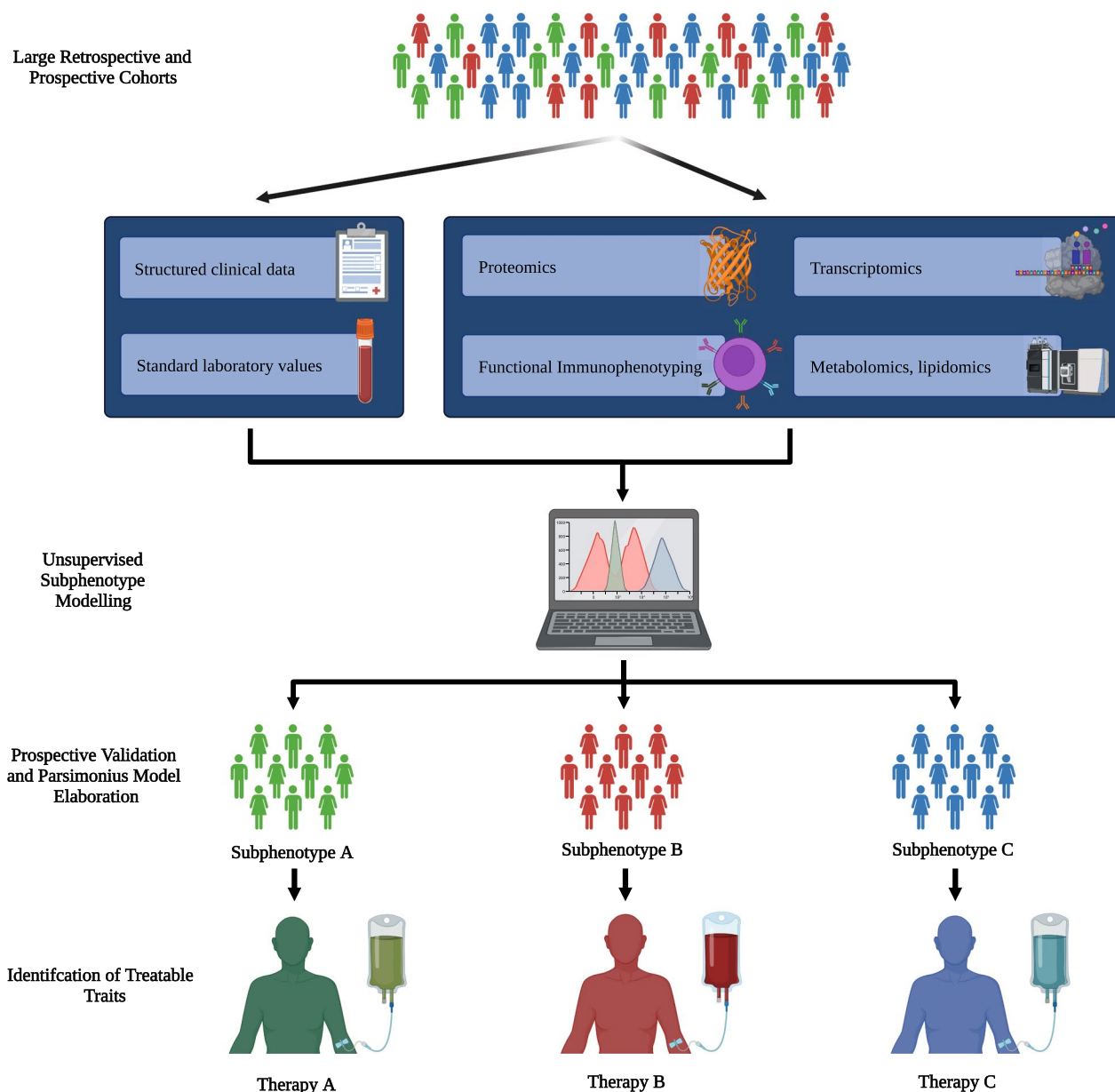
The heterogeneity of sepsis, spanning from its broad definition to the conundrum surrounding its pathophysiological inception and development, has hindered successful immunomodulatory therapies. Traditional subgrouping based on single traits or biomarkers falls short. Advances in computing and data have enabled investigating this diversity to find patient subgroups (subphenotypes) with shared characteristics, biological mechanisms, and treatment responses (Fig. 3). Modern subphenotyping relies on unsupervised clustering algorithms such as *k*-means clustering or the very prominently used latent class analysis. Briefly, these algorithms identify data clusters in multi-dimensional space to infer different subphenotypes based on these clusters, but can be influenced by cohort biases and data collection. The sepsis subphenotypes identified to date can be subdivided into two main groups:

#### Clinical subphenotypes

Several studies have undergone efforts to identify clinical subendotypes. An example is Seymour and colleagues seminal work, identifying  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  phenotypes via *k*-means clustering [116].  $\alpha$  had least organ dysfunction;  $\beta$  was older with comorbidities;  $\gamma$  and  $\delta$  showed inflammation, with  $\delta$  having higher lactate and vasoplegia. Mortality ranged from 2% ( $\alpha$ ) to 32% ( $\delta$ ), affecting intervention outcomes due to varied subphenotypes in trials. Similarly, Kudo et al. described four coagulopathy-based sepsis phenotypes, responding differently to recombinant human thrombomodulin [117]. Other studies investigated subphenotype-specific treatment responses in fluid resuscitation, antibiotic delay, temperature trajectories, progression to septic shock, and hemodynamics [118–122].

#### Biological subphenotypes

This field covers protein-based biomarkers, proteomics, immune-phenotyping, transcriptomics, and metabolomics. Three subphenotypes based on whole-blood RNA patterns showed variations in glucocorticoid signaling, immunity, and zinc balance, linked to disease severity and mortality [123]. A multiplex messenger RNA quantification platform was developed, revealing distinct responses to glucocorticoid therapy [124, 125]. Davenport et al. identified two sepsis response signatures (SRS) from blood leukocyte transcriptomic clustering [126]. SRS1 subphenotype linked to higher mortality, while SRS2 showed endotoxin tolerance and T cell exhaustion, associating with HLA class II downregulation. In VANISH trial analysis, SRS2 had increased mortality with hydrocortisone therapy [127]. Other subphenotypes include molecular diagnosis and risk stratification for sepsis



**Fig. 3** Overview of the potential research pathway leading from data to the identification of functional endotypes. First, clinical and biological data have to be collected in the framework of observational cohorts or randomized controlled trials. Critical relevance lies in the collection of samples that allow the implementation of high-throughput biological analyses in a second step. Optimally data from multiple databases are bundled in order to allow a robust subphenotype discovery. In a third step, data are fed into an unsupervised machine learning pipeline, which hopefully identifies clusters of patients in the given multi-dimensional variable constellation. These clusters or subphenotypes have then to be validated in an external prospective cohort, and optimally, a parsimonious model is then elaborated that allows identification of subphenotypes at the bedside with a minimal number of variables. Finally, and as the ultimate goal of phenotyping, a biological correlate or ideally, a treatable trait, is identified for each subphenotype, which can be targeted by means of a specific medication, leading to the transition from a subphenotype to a functional endotype

(MARS) subphenotypes from genome-wide mRNA clustering and “inflammopathic,” “adaptive,” and “coagulopathic subphenotypes from pooled transcriptomic data [128, 129]. Alternative sepsis subphenotyping methods involve flow cytometry-based immunophenotyping and

combined transcriptomic, proteomic, and metabolomic data [130, 131]. The PROVIDE trial recently investigated whether a hyperinflammatory subphenotype (identified by serum ferritin >4420 ng/mL) benefits from anakinra treatment and immunoparalyzed individuals (identified

by <5000 HLA-DR/monocytes) benefit from rhIFN $\gamma$  administration [84]. However, the 36 hyperinflammatory patients randomized to receive IL-1Ra or placebo before premature discontinuation of the study showed no difference in 28-day mortality. A follow-up study called the ImmunoSep trial with an expanded therapeutic window for the treatment of hyperinflammation by anakinra is currently recruiting [85].

### Summary and future perspectives

The sepsis syndrome arises from a complex dysregulation in the host's response to pathogens (Fig. 1). Immunotherapeutics demonstrated promising preclinical efficacy, yet clinical applicability struggles due a lack of in depth knowledge and efficient monitoring tools to individualize specific targeted treatment strategies [6]. Recognizing sepsis's heterogeneity as a key factor, initial distinct response phenotypes have been identified using both biomarkers and clinical data (Fig. 2) [116] showing their potential in post hoc subanalyses of prior negative RCTs pinpointing certain phenotypes potentially benefiting from immunotherapy [19, 116, 127]. The first prospective RCTs using biomarkers for such predictive enrichment are on the way [84, 85]. Granularity might be further raised by zooming-in on the “-omics” level describing so-called sepsis endotypes. Obviously complicated by practical implementation issues where new biomarkers that can be used in the ICU would be highly desirable (*ideally* by Point-of-Care devices). We have no doubts that identification of treatable traits through “-omics” technologies will improve our chances of a successful therapeutic immune modulation. Computational tools like artificial intelligence and machine learning approaches will leverage extensive clinical and immune data helping us to uncover such new treatable traits [132].

The role of the microbiome and host metabolism in shaping the response to infection is poorly understood. Understanding patients' immunologic and metabolic status pre-sepsis can reveal risk factors and immune balance targets. Sepsis is highly dynamic, and tracking immune changes remains challenging for tailored treatment. Longitudinal immune parameter recording, including biomarkers and cell responsiveness, will aid flexible treatment paths guiding the immune system toward optimal state [133].

It is important to acknowledge that many therapeutic concepts oversimplify sepsis by focusing solely on systemic inflammation somewhat neglecting that organ dysfunction is the common denominator that determines the transition from an uncomplicated infection to sepsis. These failing organs become dysfunctional [134] as a consequence of an insufficient tissue damage control response and mismatch of energy demands and supplies

[135, 136]. Mechanisms behind disease progression to sepsis are unclear, but protective cellular responses to stress signals, called disease tolerance to infection, reduce infection-associated consequences [137]. Serum metabolome and proteome integration in humans supports the hypothesis of a dysregulated metabolism [138]. It is of surprise that little work has been done to directly target the organ dysfunction apart from the (upstream) immune response. A first clinical phase II study that investigates repurposing epirubicin to improve tissue damage control is currently recruiting patients (EPOS-1; NCT05033808) [139]. Further potential molecular metabolic targets such as lactate, glutamine, pyruvate, or ketone bodies have been identified in translational studies, but remain to be tested in a personalized manner in clinical trials [140–143].

In our opinion, the current separation between hyperinflammation and immunosuppression is not sufficient to stratify all septic patients for immunomodulatory approaches. We need to find better ways to investigate their host responses that are physiologically not separated but rather closely linked to one another. In addition to that, we need to seek a better understanding of organ dysfunction in the large group of patients without these extreme immune-dysregulations [84, 144]. Recent advances to personalize and monitor therapies should allow us to modulate immunity and improve disease tolerance of the individual septic patient.

### Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13
APC	Activated protein C
ARDS	Acute respiratory distress syndrome
ART-123	Recombinant thrombomodulin
bioADM	Bioactive adrenomedullin
BLTA	B and T lymphocyte attenuator
COVID-19	Coronavirus disease 2019
DAMPs	Damage-associated molecular patterns
delta-SOFA score	Delta-sequential organ failure assessment score
DIC	Disseminated intravascular coagulation
EC	Endothelial cells
eGC	Endothelial glycocalyx
eNOS	Endothelial nitric oxide synthase
HLA-DR	Human leukocyte antigen-DR isotype
ICU	Intensive care unit
iNOS	Inducible nitric oxide synthase
IFN $\gamma$	Interferon gamma
IvIG	Intravenous immunoglobulins
LAG-3	Lymphocyte-activation gene 3
MARS	Molecular diagnosis and risk stratification for sepsis
mRCT	Multi-regional randomized controlled trials
MSC	Mesenchymal stem cell
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
RCT	Randomized controlled trial
SoC	Standard of care
SRS	Sepsis response signature
suPAR	Soluble urokinase-type plasminogen activator receptor
TA1	Thymosin alpha 1

TPE	Therapeutic plasma exchange
TTP	Thrombotic thrombocytopenic purpura
VSMC	Vascular smooth muscle cells
VWF	Von Willebrand factor

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### Author contributions

CB, SW, AS, PWG, and SD prepared all manuscript drafts and were involved in reviewing and editing, including the tables and figures. CB and SD conceived the concept underlying the manuscript and were involved in editing of the manuscript, including the tables and figures. All authors approved the final version of the manuscript.

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