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From immune heterogeneity to precision medicine in sepsis

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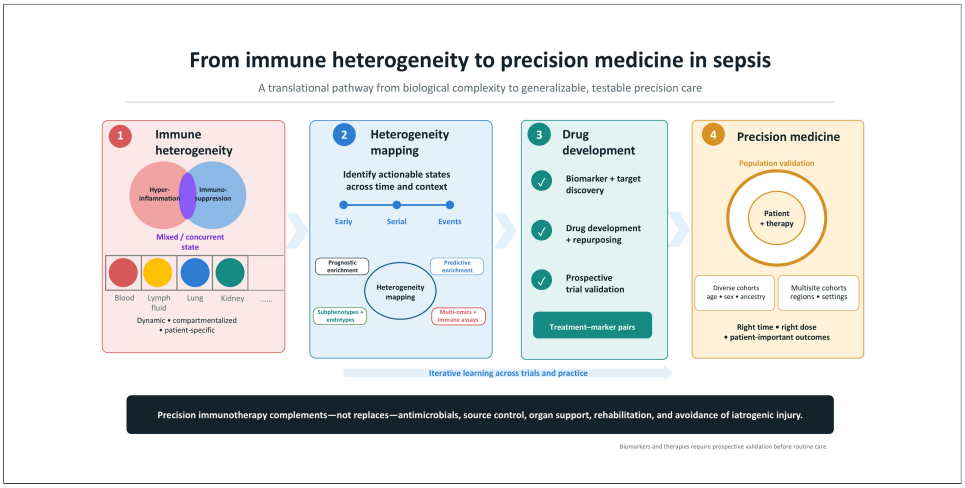

INTRODUCTION

Kox *et al.* recently published a comprehensive review in *Nature Reviews Nephrology*, providing a timely and thorough summary of sepsis immunobiology[1]. While Kox *et al.*[1] provide an elegant synthesis of current concepts in sepsis immunobiology, the review also inadvertently underscores a persistent translational gap: despite substantial conceptual progress, the field still lacks robust evidence that these frameworks meaningfully improve patient outcomes in real-world clinical settings. Our specific perspective is that the next step is not another sepsis taxonomy, but an actionability test: a proposed endotype should demonstrate biological validity across time and compartments, prospectively identify differential response to a specified therapy, and return an interpretable result within the clinical decision window. This

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decision-focused standard frames the discussion that follows.

RESHAPING CONCEPTUAL FRAMEWORKS: MOVING BEYOND SIMPLE INFLAMMATION AND SUPPRESSION

Sepsis is currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. As the authors insightfully highlight, pro-inflammatory and anti-inflammatory pathways are often activated simultaneously rather than sequentially. Hyperinflammation and immunosuppression frequently coexist. The compartmentalization phenomenon further complicates the picture: sepsis involves multi-organ injury, and detection based solely on blood samples may fail to reflect tissue-specific responses. Metabolic reprogramming and long-term sequelae further exacerbate the complexity of the sepsis disease course.

The article emphasizes moving away from the traditional binary paradigm of "hyperinflammation versus immunosuppression" toward a more nuanced understanding of the dynamic, compartmentalized, and highly heterogeneous host response[1]. This perspective is highly consistent with evidence accumulated from multiple independent cohort studies[2-5] and explains why "one-size-fits-all" immunomodulatory trials have largely failed, while paving the way for predictive enrichment and personalized interventions[6,7]. Nevertheless, these conceptual frameworks remain difficult to operationalize in clinical practice, and robust bedside tools to translate these theoretical constructs into real-time decision support are still lacking. Accordingly, reproducible prognostic separation should not be equated with treatment-predictive utility.

PROSPECTS AND CHALLENGES OF ENRICHMENT STRATEGIES

Kox *et al.* emphasize the balanced application of prognostic and predictive enrichment. Prognostic tools can identify high-risk patients but cannot guarantee response to specific therapies[1]. Predictive enrichment has shown promising signals in secondary analyses: hyperinflammatory Acute Respiratory Distress Syndrome (ARDS) subphenotypes benefit from simvastatin or fluid management, while the efficacy of glucocorticoids depends on sepsis response signatures (SRS) subtype or inflammatory status. These observations are hypothesis-generating and should not be presented as equivalent to prospectively validated precision therapy in sepsis. Several biomarker-guided therapeutic strategies have been proposed, aiming to translate immune heterogeneity into actionable interventions [Table 1]. These approaches span diverse biological states, including hyperinflammation, immunoparalysis, complement activation, and metabolic dysfunction. However, most remain supported by subgroup analyses, mechanistic studies, or early-phase trials, highlighting the substantial gap between biological plausibility and clinical implementation. Among these strategies, biomarkers such as mHLA-DR, suPAR, and ferritin have provided proof-of-concept for theragnostic approaches. Nevertheless, their clinical utility remains uncertain because most findings derive from post hoc analyses, and prospective randomized validation is still limited.

A systematic review of predictive enrichment using biomarkers in sepsis also supports this view[64]. It identified 12 eligible randomized studies, all using single circulating protein or endotoxin biomarkers for predictive enrichment. Although five studies reported statistically significant primary outcomes, only two showed patient-important benefits. Only five used point-of-care assays, and none incorporated genetic, transcriptomic, or metabolomic markers, underscoring the narrow scope and limited clinical translation of current biomarker-guided strategies in sepsis trials. Beyond these limitations, challenges remain prominent: sepsis phenotypes exhibit significant dynamism, with one study showing that up to 46% of baseline phenotypes undergo substantial changes by days 3 and 5[65], posing a major challenge for enrichment strategies reliant on single time-point assessments. Subphenotype studies also face a lack of standard assays with harmonized reliability and reproducibility; insufficient simultaneous assessment of multi-omics and non-omics responses across compartments[66]; and, as noted in the review, marked compartmentalization of

Table 1. Candidate therapies organized by immune state and biological process in sepsis

ID	Immune state/biological process	Putative beneficiary or risk subgroup	Biomarker/selection rule	Candidate intervention	Biological rationale	Evidence level/key finding	Translational barrier/safety	References
H1	Hyperinflammation (predictive-enrichment example)	SRS2/immune-adaptive state may identify harm from corticosteroids; in COVID-19 benefit varies with oxygen requirement and inflammatory subgroup	SRS2 transcriptomics; immune-adaptive gene-expression score; oxygen/mechanical ventilation; hyper-/hypoinflammatory class	Corticosteroids/dexamethasone	Broad anti-inflammatory action; the review emphasizes directionally different effects across subgroups	Human RCTs plus post hoc subgroup analyses: higher mortality with corticosteroids in VANISH SRS2/immune-adaptive groups; benefit in oxygen-requiring, especially ventilated, COVID-19	Mostly post hoc subgroup effects; infection and compartment dependence; prognostic enrichment alone is insufficient	[1,8-11]
H2	Hyperinflammation (cytokine-driven)	Patients with COVID-19 and higher IL-6; no non-COVID-19 sepsis threshold is provided	Circulating IL-6 (no threshold stated)	Tocilizumab	IL-6 inhibition; also discussed in a C5a-IL-6 combination rationale	The review states that higher-IL-6 COVID-19 patients may be more likely to respond; combination signal with vilobelimab is from post hoc phase III analysis	Limited generalization to non-COVID-19 sepsis; unvalidated threshold; combination requires prospective testing	[1,12-15]
H3	Hyperinflammation (ARDS-like subgroup)	Retrospectively identified hyperinflammatory ARDS subgroup	Latent-class model using clinical variables plus plasma proteins; no bedside cut-off listed here	Simvastatin	Potential modulation of hyperinflammation	Secondary analysis of HARP-2 RCT: improved 28- and 90-day survival in hyperinflammatory subgroup; no difference in hypoinflammatory subgroup	Post hoc subgroup in ARDS; real-time classifier and prospective validation lacking	[1,16,17]
H4	Hyperinflammation/coagulopathy (historical enrichment example)	Hyperinflammatory septic-shock subgroup; possible harm in hypoinflammatory subgroup	Hyper-/hypoinflammatory classification; no single cut-off	Activated protein C (APC)	Anticoagulant and inflammation-modulating example of treatment-effect heterogeneity	Secondary PROWESS-SHOCK analysis: mortality 32% *vs.* 39% in hyperinflammatory subgroup; 23% *vs.* 17% in hypoinflammatory subgroup, suggesting harm	Secondary analysis with opposite subgroup effects; presented as enrichment evidence, not a current recommendation	[1,5,18,19]
H5	Hyperinflammation/MALS	MALS; hepatobiliary dysfunction plus DIC; high IL-1RA; or high suPAR in COVID-19	Ferritin > 4,420 ng/mL (PROVIDE/ImmunoSep); IL-1RA > 2,071 pg/mL; suPAR ≥ 6 ng/mL (COVID-19)	Anakinra	IL-1 receptor blockade to suppress hyperinflammation	Unselected sepsis phase III RCT stopped for futility; mortality signals in post hoc MALS/high-IL-1RA subgroups; SAVE-MORE was a biomarker-enriched COVID-19 RCT	Core sepsis signals are post hoc; thresholds/phenotypes need prospective validation; COVID-19 generalizability is limited	[1,20-23]
H6	Hyperinflammation/JAK-STAT activation	Hyper-/hypoinflammatory ARDS classes planned for PANTHER; no sepsis-specific companion diagnostic is provided	Inflammatory class; IL-6 is pathway-related but not specified as a treatment cut-off	JAK-STAT inhibitors, especially baricitinib	Blocks cytokine-receptor downstream signaling; may protect against kidney injury	COVID-19 meta-analysis: mortality about 14% to 12%; PANTHER planned to stratify by inflammatory class	Infection, venous thrombosis, skin malignancy and gastrointestinal perforation risks; discontinuations in severe pediatric COVID-19; limited general-sepsis evidence	[1,24-27]
C1	Complement activation/thromboinflammation	High C5a with hyperinflammation and thrombosis; invasively ventilated COVID-19 is the studied outcome population	Activated complement C5a; no treatment threshold stated	Direct C5a inhibitor vilobelimab; eculizumab is discussed as an upstream-inhibitor limitation	Blocks C5a while preserving C5b and membrane-attack-complex formation, aiming to reduce inflammation/thrombosis while retaining host defence	Phase III COVID-19 trial: lower all-cause mortality and kidney replacement therapy; severe sepsis/shock study suggested preserved membrane-attack-complex lysis	Possible impaired microbial clearance and bleeding; COVID-19 generalizability; upstream blockade may miss thrombin-generated C5a	[1,13,28-30]

M1	Metabolic dysfunction/pro-inflammatory metabolic reprogramming	Monocyte/lymphocyte shift from FAO to aerobic glycolysis; no validated selection subgroup	No bedside metabolic biomarker is proposed for metformin selection	Metformin	Modulates mitochondrial complex I, AMPK and redox state; may shift toward FAO and reduce TLR4-NF-κB, inflammasome activation and inflammatory mediators	Animal models plus retrospective clinical studies; four randomized sepsis trials underway	Accumulation, hyperlactatemia and metabolic acidosis in severe renal impairment; early glycolysis suppression may weaken antimicrobial responses	[1,31-34]
I1	Immunoparalysis/monocyte deactivation	Sepsis-associated immunosuppression with persistently low mHLA-DR	mHLA-DR < 8,000 monoclonal antibodies/cell for 2 days	GM-CSF	Stimulates myeloid/monocyte function and restores HLA-DR and TLR2/4-induced cytokine production	Small biomarker-selected randomized trial, n = 38: mHLA-DR normalized in 19/19 *vs.* 3/19; shorter ventilation, ICU and hospital time	Small sample; broad activity; may drive pathological myelopoiesis and MDSCs, worsening adaptive suppression	[1,35,36]
I2	Immunoparalysis/endotoxin tolerance	Low mHLA-DR with ferritin below the MALS threshold	mHLA-DR < 5,000 mABs/cell plus ferritin < 4,420 ng/mL (PROVIDE/ImmunoSep)	IFNγ	Activates macrophages, counters endotoxin tolerance and restores mHLA-DR and monocyte TNF production	Mechanistic signals in repeated human endotoxemia and open-label sepsis studies; PROVIDE n = 36 with only 1 IFNγ recipient; ImmunoSep n = 280 unpublished at review publication	Clinical outcome effects cannot be assessed robustly; thresholds need validation; broad pro-inflammatory action may be unsuitable when hyperinflammation coexists	[1,23,37-39]
I3	Immunosuppression/profound lymphopenia	Apoptosis-dependent lymphocyte loss and profound lymphopenia	Reduced lymphocyte count; low IL-7 receptor mRNA is prognostic but not a validated selection cut-off	IL-7/CYT107; IL-7-Fc virotherapy	Anti-apoptotic; improves CD4+ and CD8+ T-cell survival, expansion and proliferation	Experimental bacterial/fungal sepsis; proof-of-principle septic-shock and COVID-19 studies reversed CD4/CD8 loss; *ex vivo* T-cell restoration	Mostly mechanistic/proof-of-principle evidence; no outcome evidence or validated cut-off	[1,40-43]
I4	Immunosuppression/T-cell exhaustion	PD1/PDL1/CTLA4-associated exhausted T-cell phenotype	Elevated soluble PDL1 is associated with mortality; no treatment-selection cut-off is provided	Anti-PD1 or anti-PDL1	Releases checkpoint inhibition and enhances T-cell function	Benefits in sepsis models; phase I anti-PDL1 sepsis trial was well tolerated and achieved full receptor occupancy at day 28 with a single 900-mg dose	Early safety/pharmacodynamic evidence only; rash, autoimmune thyroiditis/colitis and systemic hyperinflammatory syndrome	[1,44-47]
I5	Immunosuppression/secondary-infection susceptibility (trained immunity)	Potentially patients at risk of secondary bacterial or fungal infection; no clinical endotype defined	No validated selection biomarker proposed	β-glucan	Acts through dectin-1/complement receptor 3 and can induce trained immunity	Potential-benefit evidence is limited to animal studies	No human safety, dose, timing or outcome evidence; possible risk when hyperinflammation coexists	[1,48-51]
D1	Dual/time-dependent immune dysregulation and platelet activation	Short-term exposure may enhance innate immunity; chronic exposure may reduce inflammation and promote lipid-mediator resolution	No selection biomarker proposed	Low-dose aspirin	Chronic: suppresses TNF, enhances lipid-mediator resolution and inhibits platelets; acute: pro-inflammatory effect in LPS challenge	Short-term human LPS challenge; observational meta-analysis signal; large RCT in adults > 70 showed no reduction in sepsis-related death	Direction depends on timing; large RCT does not support primary prevention; deterioration prevention/secondary prevention remain research questions	[1,52-55]
R1	Microbiome disruption/barrier and inflammatory dysregulation	Gut dysbiosis and lost colonization resistance; post-ICU secondary-infection/long-term-complication risk is a research target	No validated bedside microbiome/metabolite threshold proposed	Next-generation probiotics, fecal microbiota transplantation, short-chain fatty acids/indoles	Restore microbiota/barrier; metabolites can inhibit cytokine production	Untargeted Lactobacillus/Bifidobacterium RCTs negative; FMT supported by case reports/animals; metabolites by inflammation/sepsis animal models	Safety/controllability of live organisms; no human validation, selection rule, dose or timing standard	[1,56-59]
X1	Multiaxis hyperinflammation (C5a-IL-6-JAK/STAT loop)	Concurrent complement and IL-6/JAK-STAT activation; no validated endotype	C5a, IL-6 and related pathway measures; no combined cut-offs specified	Vilobelimab + tocilizumab; or vilobelimab + baricitinib	Interrupts the C5a-IL-6-STAT3 feedback loop	Vilobelimab-tocilizumab survival synergy is from post hoc phase III analysis; baricitinib combination is mainly mechanistic/preclinical	Post hoc/mechanistic evidence; combined infection/immunosuppression risk; needs prospective combination trials and companion diagnostics	[1,13-15]

G1	Endothelial injury/immunothrombosis (evidence gap)	Endothelial activation, leukocyte adhesion/transmigration, thrombin formation and platelet activation	No validated endothelial-treatment selection biomarker is proposed	No dedicated endothelial-repair drug appears in the future-candidate list; aspirin/complement inhibition are adjacent platelet/thromboinflammatory strategies only	Endothelial activation connects inflammation and coagulation, but no direct treatment-biomarker pair is provided	Mechanistic discussion; no dedicated candidate clinical evidence in this review	No companion diagnostic or direct intervention; adjacent-mechanism drugs should not be presented as validated endothelial therapy	[1]
G2	Failed inflammation resolution/tissue repair (evidence gap)	Post-sepsis low-grade chronic inflammation, impaired resolution and insufficient regeneration/repair	The review explicitly states that validated biomarkers for this inflammatory state are lacking	No dedicated pro-resolving/tissue-repair candidate is listed; chronic low-dose aspirin is only described as enhancing lipid-mediator resolution	Pro-resolving mediators, macrophage polarization, efferocytosis, angiogenesis and cellular regeneration are candidate processes	Conceptual/mechanistic framework; no targeted clinical trial described in this review	No validated biomarker; tolerance, repair and resolution biology remains early; long-term outcomes and treatment window are unclear	[1,60-63]

RCTs: Randomized controlled trials; VANISH: effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock; ARDS: acute respiratory distress syndrome; PROWESS-SHOCK: drotrecogin alfa (activated) in adults with septic shock; MALS: macrophage activation-like syndrome; PROVIDE: toward personalized immunotherapy in sepsis; DIC: disseminated intravascular coagulation; SAVE-MORE: interferon gamma-induced protein 10 (IP-10) for the early prognosis of the risk for severe respiratory failure and death in COVID-19 pneumonia; JAK-STAT: Janus Kinase-signal transducer and activator of transcription; PANTHER: platform adaptive trial of novel therapies in the hyper- and hypo-inflammatory endotypes of ARDS; FAO: fatty acid oxidation; AMPK: AMP-activated protein kinase; TLR4-NF-κB: toll-like receptor 4-nuclear factor kappa B; mHLA-DR: monocyte human leukocyte antigen-DR; GM-CSF: granulocyte-macrophage colony-stimulating factor; HLA-DR: human leukocyte antigen-DR; ICU: intensive care unit; MDSCs: myeloid-derived suppressor cells; IFNγ: interferon gamma; TNF: tumor necrosis factor; LPS: lipopolysaccharide; FMT: fecal microbiota transplantation.

the host response, where blood-based biomarkers often fail to reflect the local immune status in target organs such as the lungs and kidneys, potentially leading to mis-stratification when relying solely on peripheral blood detection.

Most subphenotype and endotype studies still rely on retrospective cohorts, with insufficient prospective validation. Currently, there is also a lack of rapid, reliable point-of-care testing technologies in clinical practice, making it difficult to meet the urgent time-sensitive demands of sepsis diagnosis and treatment[64]. As a pragmatic research framework, an initial state estimate could be obtained within 6 h, repeated at approximately 24-48 h, and reassessed at days 3-5 in patients with persistent or worsening organ dysfunction, with event-triggered testing for recurrent shock, secondary infection, or new organ injury. These intervals are proposed for prospective testing, not as a validated clinical standard. Any dynamic algorithm should prespecify how indeterminate results, blood-organ discordance, biomarker normalization, and safety-based stop or switch decisions will be handled.

Host transcriptomic endotypes have revealed differences in adaptive immunity, innate inflammation, endothelial activation, coagulation, and metabolism[3-5]. A recent consensus analysis reconciled major blood transcriptomic systems into three subtypes using the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) and the Genomic Advances in Sepsis (GAinS) cohorts, including longitudinal samples[67]. Host genetic variation can also shape the sepsis transcriptomic response: an analysis of 638 adults identified 16,049 independent expression quantitative trait loci and genotype-by-endotype interactions[68]. Beyond transcriptomic regulation, genetic causal-inference approaches may help prioritize candidate biomarkers. For example, an observational and two-sample Mendelian randomization study reported an association between higher serum alkaline phosphatase levels and sepsis susceptibility, although its utility for immune endotyping or treatment prediction remains unestablished[69]. Together, these findings support mechanism discovery and biomarker prioritization, but neither molecular association nor Mendelian randomization evidence alone

establishes an actionable endotype or predicts treatment response.

Longitudinal integration of transcriptomics, proteomics, metabolomics, and functional immune assays may better capture transitions than a single baseline measurement[70]. However, additional molecular layers are useful only if they improve a prespecified decision beyond routine clinical data, can be measured within the treatment window, and retain calibration across populations.

EMERGING THERAPIES AND TRIAL INNOVATION

The review highlights several repurposed and novel agents: Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) inhibitors, metformin, selective Complement Component 5a (C5a) inhibitors, Interleukin-7 (IL-7), anti- Programmed Death (Ligand)-1 [PD(L)1] monoclonal antibodies, and β-glucan-induced trained immunity. These agents target specific nodes in the inflammatory process and align with conceptual frameworks such as resistance, tolerance, resolution, and repair. Combinations (e.g., C5a + IL-6 blockade) merit exploration given pathway crosstalk.

Sepsis drug development has faced long-standing difficulties, with most randomized controlled trials ending in failure. The primary reasons include extreme patient heterogeneity, limitations of single-target interventions, lack of reliable predictive biomarkers, and the inability of traditional fixed-design trials to address the dynamic disease course[71,72]. On ClinicalTrials.gov, three randomized controlled trials on precision immunotherapy for sepsis are currently registered: ImmunoSep, titrated administration of IgM-enriched preparation, and Adaptive Platform Trial for Personnalisation of Sepsis Treatment in Children and Adults (PALETTE). The results of the ImmunoSep trial were published in *JAMA* this year, demonstrating the importance of precision immunotherapy: researchers personalized treatment with anakinra or recombinant interferon-γ according to patients' immune status, and the precision immunotherapy group showed significantly better improvement in organ function and infection clearance compared with the placebo group. Its prespecified primary endpoint-a decrease of at least 1.4 points in mean Sequential Organ Failure Assessment (SOFA) score from baseline through day 9-was achieved in 35.1% of patients assigned to immune-status-guided therapy and 17.9% assigned to placebo {difference, 17.2% [95%CI, 6.8% to 27.2%]; P = 0.002}. Mortality at 28 days was not statistically significantly different between groups[73]. Results from the other two trials have not yet been published. Independent replication, assay standardization, and external validation are required before routine implementation.

Most current evidence supporting sepsis phenotyping and precision immunotherapy is derived from European and North American cohorts. However, substantial inter-population variability in genetic background, comorbidity patterns, pathogen distribution, and healthcare systems may limit the direct generalizability of these findings to Asian populations. In addition, differences in baseline immune status and treatment accessibility may further influence biomarker performance and enrichment strategy effectiveness. Therefore, region-specific validation in Asian critically ill populations is urgently required to ensure the global applicability of precision medicine approaches. We briefly note the CMAISE (Chinese Multi-omics Advances in Sepsis) database as an emerging longitudinal multi-omics resource that may support future mechanistic and translational studies in Asian critically ill populations[74]. Across 43 Chinese centers, multi-omics profiling has been completed for 1,284 patients meeting Sepsis-3 criteria, generating more than 4,500 samples at principal time points on days 1, 3, and 5 and integrating transcriptomic, proteomic, metabolomic, single-cell, and dense clinical data. Multi-omics initiatives such as CMAISE may help address this gap by enabling population-specific model development and validation.

The core future directions for sepsis treatment include: establishing dynamic, multidimensional stratification systems that integrate clinical phenotypes, molecular endotypes, and treatable traits to achieve real-time

precision intervention; developing point-of-care rapid multi-omics detection combined with artificial intelligence-assisted decision-making systems to overcome the limitations of traditional single-time-point detection and static stratification; and promoting adaptive platform trials and embedded study designs to accelerate clinical validation of multi-target combined immune modulation strategies.

SUMMARY AND OUTLOOK

Kox *et al.*'s[1] article clearly declares that sepsis immunology has moved beyond the era of simple binary classification. The realization of precision medicine depends on three pillars: first, deepening the understanding of core mechanisms such as immune resistance, disease tolerance, resilience, resolution and repair; second, using multi-omics technologies and artificial intelligence to identify reliable, dynamic, and point-of-care detectable "treatable traits"; and third, adopting flexible and efficient clinical trial designs, such as adaptive platform trials and Bayesian methods, to simultaneously evaluate multiple therapies targeting specific endotypes.

The main future challenge lies in how to systematically integrate these insights into clinical practice and develop "combination" precision treatment regimens that can act at different time points, target different individuals, and affect different tissues and organs. For critical care physicians and researchers, this is a pivotal moment to abandon "one-size-fits-all" thinking and embrace the complexity and precision of the disease. Correction of immune dysregulation alone is unlikely to restore established multiorgan dysfunction; antimicrobial therapy, source control, lung-protective ventilation, hemodynamic optimization, renal support, nutrition, rehabilitation, and avoidance of iatrogenic injury must proceed in parallel. Precision immunotherapy should therefore be judged by reproducible patient-important outcomes, not biomarker normalization alone.

DECLARATIONS

Authors' contributions

Conceptualization: Jin X, Zhang Z
Writing-original draft: Jin X
Writing-review and editing: Yang J, Yang S, Zhang Z
Supervision: Zhang Z
All authors read and approved the final manuscript.

Availability of data and materials

Not applicable.

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During the preparation of this manuscript, the AI tool ChatGPT (version GPT-5.6, released 2026-07-09) was only employed to enhance the readability and language quality of the manuscript and provided assistance during the preparation of Graphical Abstracts. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Ethical approval and consent to participate

Not applicable.

Consent for publication

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