

LITERATURE REVIEWS

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Sepsis: deciphering pathogenesis and transforming diagnosis and treatment through systems immunology

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Abstract

Background. Sepsis is responsible for over 11 million deaths per year, constituting one of the most heterogeneous critical illness syndromes. Whilst the implementation of bundle-based care has been demonstrated to be efficacious in reducing mortality, this effect has been shown to plateau in well-resourced settings due to the presence of biological heterogeneity. Systems immunology methods have been demonstrated to offer significant potential for the development of precision diagnosis and treatment strategies.

Objective. The objective of this study was to undertake a systematic review of the extant evidence on systems immunology in the context of sepsis diagnosis and treatment. In addition, the study will involve a critical analysis of the limitations of the leading conceptual frameworks in this area, and the delineation of future research priorities.

Materials and methods. A systematic analysis and synthesis of 43 publications from PubMed/MEDLINE, Cochrane Library, and Frontiers (2016–2025) was conducted, with priority given to retrospective analyses of randomized controlled trials (RCTs), systematic reviews, and large-cohort studies ($n > 100$). The following keywords were utilised: 'sepsis endotypes', 'phenotypes', 'precision medicine', and 'transcriptomics'. The protocol was registered in the international registry of systematic reviews PROSPERO (CRD420261347322). Images were created using the Nano Banana 2.0 AI image editor (<https://nano-banana2.co/>), and the resulting data were reviewed, with changes and corrections made by the authors in accordance with the literature reviewed in this article.

Results. Hancock et al. (2024) identified five distinct endotypes, each characterised by approximately 200 unique differentially expressed genes, in transcriptomic data from emergency department patients (before formal diagnosis). The five types of inflammation are as follows: NPS (Neutrophilic–Suppressive): the most deadly type, and a potential target for dexamethasone; INF (Inflammatory): characterised by hyperinflammation, opposed to NPS; IFN (Interferon): the predominance of interferon pathways; ADA (Adaptive): involving adaptive immunity; and IHD (Innate Host Defence): the activation of natural host defence. The SUBSPACE consortium (2025, $n=3,380$) validated four consensus endotypes and proposed the Hi-DEF two-dimensional framework (OR for severe outcomes with system-wide dysregulation=7.1, 95%CI 5.6–8.9). RCTs confirmed heterogeneity of treatment effect: corticosteroids, simvastatin, and activated protein C demonstrated differential effects by subphenotype.

Conclusions. Systems immunology is transforming the management of sepsis, moving away from universal bundle protocols towards precision strategies. Key future priorities include prospective endotype-enriched adaptive RCTs, the development of bedside-compatible diagnostics, and improvements in global accessibility.

Keywords: sepsis, systems immunology, endotypes, transcriptomics, precision medicine, machine learning, immunotherapy, and Covid-19.

Introduction

Sepsis is defined as an abnormal, life-threatening response to infection that leads to (multi)organ dysfunction [1]. Its global burden is significantly higher than was previously thought: an estimated 48.9 million cases and 11 million deaths were reported in 2017, accounting for 19.7% of all deaths worldwide [2]. The incidence and mortality rates of sepsis vary significantly between regions, with the greatest

burden falling on low-income countries. Post-sepsis, physical, cognitive, and psychological sequelae have been observed in up to 40% of survivors. Moreover, more than 70% of patients who survive their initial episode of sepsis are readmitted to the hospital within the subsequent year [3, 4].

In its most severe form, the novel coronavirus (SARS-CoV-2) shares striking parallels with severe sepsis [5, 6]. Systemic immunology studies have identified various mo-

lecular markers common to patients with both severe acute respiratory syndrome (SARS) and sepsis. After a week in the intensive care unit (ICU), these groups become indistinguishable in terms of gene expression profiles [7]. This underscores the significance of sepsis-oriented approaches in the context of pandemic preparedness.

The prevailing approach to the management of sepsis centres on the administration of antimicrobial agents and the provision of supportive care measures. However, these interventions do not address the intricate immune system dysfunctions that underpin the condition, nor do they take into account the variability in presentation of sepsis among patients and the temporal dynamics of the condition. For a period of more than twenty years, advances in the field of healthcare have been observed to have reached a state of stagnation in high-income healthcare systems [8]. A plethora of clinical trials, numbering over one hundred, have been conducted on pharmaceuticals that modulate the immune response. These trials have incurred costs amounting to hundreds of millions of dollars, yet they have not yielded consistent clinical efficacy [9]. Systems immunology, a field encompassing the computational analysis of the immune system as a complex biological system, is beginning to transform this paradigm [9].

The subject of sepsis endotypes represents a highly dynamic area of modern resuscitation medicine. While the total number of articles on sepsis is increasing exponentially, interest in its endotypes (the division of patients into groups based on biological characteristics) has increased exponentially in recent years. The question that needs to be addressed is why such rapid growth has been observed. This can be explained by three factors. Firstly, the failure of a universal approach, whereby scientists have finally recognised that 'sepsis is not a single disease' and that testing drugs on all patients in a row does not work. Secondly, a technological

breakthrough, whereby the availability of Omics methods (transcriptomics, proteomics, metabolomics) has made it possible to see biological differences between patients who appear clinically identical. Thirdly, the use of artificial intelligence, with most articles from 2023–2025 using cluster analysis and neural networks to automatically determine the type of sepsis in real time.

This review aimed to summarize the current data (2016–2025) on the use of systemic immunology methods to understand the pathogenesis of sepsis and develop new diagnostic approaches and treatment strategies, with a critical analysis of existing concepts in light of the latest research (2024–2025).

Materials and methods

In order to prepare this review, a systematic search and analysis of scientific publications in the PubMed/MEDLINE, Cochrane Library, and Frontiers databases for 2016–2025 was conducted. The following keywords were utilised: 'sepsis endotypes', 'phenotypes', 'precision medicine', 'transcriptomics', and 'COVID-19 sepsis'. The terms subphenotypes and theragnostics are also of relevance in this context. Preference was given to randomised controlled trials (RCTs), systematic reviews, meta-analyses, and cohort studies with a sample size of more than 100 patients. A total of 43 primary sources were analysed; the inclusion criteria were full-text availability and the presence of a DOI.

Results

1. Early diagnosis of sepsis: from clinical criteria to genomic signatures.

The current diagnosis of sepsis is based on the Sepsis-3 criteria (2016), which require a suspected or confirmed infection and an increase in the SOFA score of at least 2 points [1]. However, the limited sensitivity of the qSOFA score, estimated at only 46%, means that more than half of patients

Table 1. **Comparative characteristics of diagnostic transcriptomic signatures of sepsis (Hancock et al. 2024, adapted from [9])**

Signature	Number of genes	Comparison	AUC in sepsis	% AUC in other diseases
CR (cell reprogramming)	31	SOFA-classified sepsis	84	54
SepsetER	6	Abbreviated version of CR	83	52
IMX-BVN3	29	Bacterial vs viral	81	58
SMS (Sepsis MetaScore)	11	Sepsis vs non-infectious inflammation	74	50
Inflammatory	93	Non-specific inflammatory signature	74	52
Lukaszewski	7	Infection vs SIRS (–)	74	49
Sweeney (FAIM3:PLAC8)	2	Relationship between two genes	70	57
MS1 (Monocyte State 1)	8	Bacterial sepsis (scRNA-Seq)	68	48
SeptiCytte Rapid	2	Infectious vs non-infectious	63	52
Note: AUC — area under the ROC curve; higher values for sepsis and values close to 50% for other diseases indicate better specificity. The analysis was performed on 7 public datasets (1661 patients).				

with sepsis may not be identified promptly [13]. This limitation is clinically important, as each hour of delay in appropriate antibiotic therapy in septic shock may increase mortality by 7.6% [9]. In addition, blood culture, the conventional gold standard for pathogen identification, remains negative in approximately 50% of sepsis cases [14].

Against this background, whole-blood transcriptomic signatures have emerged as a promising strategy for earlier and more precise diagnosis. A comparative analysis of seven public datasets comprising 1,661 patients is presented in *Table 1*. Among the evaluated signatures, two showed particular diagnostic value: the Cellular Reprogramming (CR) signature, consisting of 31 genes and achieving an AUC of 84%, and SepsetER, a condensed six-gene version of the CR model with an AUC of 83% [9, 16]. Both signatures are based on the concept of monocyte “cellular reprogramming” following repeated Toll-like receptor stimulation.

Functionally, CR monocytes exhibit impaired antigen presentation, dysregulated cytokine production, and reduced capacity to regulate T-cell responses. Specifically, they are characterised by increased expression of TGF- β and IL-10 and decreased IFN- γ production [9]. In a study of dexamethasone treatment in patients with severe COVID-19, five of the six CR markers were elevated in monocytes from patients who died despite therapy, suggesting that this signature may also have value as a biomarker of treatment response [9].

A major step toward clinical implementation was the development and FDA authorization of Sepsis ImmunoScore (Prenosis, 2024), the first AI-based diagnostic tool approved for sepsis in routine practice [17]. In parallel, researchers at the University of British Columbia reported a portable bedside test in 2025 with an accuracy exceeding 90%, thereby opening the possibility of prehospital diagnosis [18]. Unlike RNA-Seq-based approaches, these tools rely on machine-learning analysis of routine clinical and laboratory variables, substantially reducing diagnostic time and cost.

2. Sepsis endotypes: from heterogeneity to precision strategies.

One of the major contributions of systems immunology has been the demonstration that sepsis is not a single disease entity but rather a syndrome composed of biologically distinct subtypes [9, 19]. The application of machine-learning approaches, particularly unsupervised clustering, has enabled the identification of sepsis endotypes defined by specific patterns of differential gene expression.

2.1. Endotypes identified by Baghela and Hancock (2022–2024).

Transcriptomic profiling of emergency department patients, performed before formal diagnosis, revealed five endotypes, each characterized by approximately 200 unique differentially expressed genes [20]. These endotypes were designated NPS (Neutrophilic-Suppressive), INF (Inflammatory), IFN (Interferon), ADA (Adaptive), and IHD (Innate Host Defence). NPS is associated with immunosuppression, the highest mortality, and potential responsiveness to dexamethasone. INF represents the opposite extreme, with pronounced hyperinflammation. Interferon-related pathways dominate IFN, ADA is associated with adaptive immune activation, and IHD reflects activation of innate host defence mechanisms [9, 20].

Several influential classification systems had been proposed before or alongside the Hancock framework. These include SRS1/SRS2 [15], MARS1–4 [21], the inflammopathic/adaptive/coagulopathic model [22], and the clinical $\alpha/\beta/\gamma/\delta$ phenotypes [23]. A comparative overview of these major endotyping systems is provided in *Table 2*. Despite differences in methodology, cohort composition, and gene selection, these frameworks converge on a common observation: endotypes characterized by exaggerated inflammation and/or impaired adaptive immunity are consistently associated with poorer outcomes [9].

Table 2. Comparison of leading classification systems for sepsis endotypes

System	Authors, year	Number of endotypes	Data type	Key clinical significance
SRS1/SRS2	Davenport et al., 2016 [15]	2	Blood transcriptomics	Differential response to corticosteroids
MARS1–4	Scicluna et al., 2017 [21]	4	Blood transcriptomics	Prognostic stratification
Inflammopathic/ Adaptive/ Coagulopathic	Sweeney et al., 2018 [22]	3	Transcriptomics (3 cohorts)	Identification of key immune mechanisms
$\alpha/\beta/\gamma/\delta$	Seymour et al., 2019 [23]	4	Clinical variables	Differential response to EGDT
NPS/INF/IFN/ADA/IHD	Baghela, Hancock, 2022–2024 [9, 20]	5	RNA-Seq (emergency department)	Prognosis, potential therapeutic targets
Hi-DEF (2D)	Moore et al. (SUBSPACE)2025 [24]	4 + continuum	scRNA-seq, bulk (3,380 patients)	Predictor of mortality OR=5.2–7.1

Note: EGDT — early goal-directed therapy; OR — odds ratio; CI — confidence interval.

2.2. The Hi-DEF consensus framework developed by the SUBSPACE consortium (Moore et al., 2025).

A major conceptual advance in endotype research was provided by the SUBSPACE consortium, whose work was published in Nature Medicine in 2025 [24]. By integrating 1,460 blood samples from 19 public cohorts and applying co-normalization using COCONUT, the investigators identified four consensus gene-expression clusters. These findings were subsequently validated in an independent cohort of 3,380 patients from 12 cohorts across 10 international centres. The resulting clusters were grouped into “detrimental” and “protective” categories, corresponding to worse and better prognostic profiles, respectively [24].

Using single-cell RNA sequencing of 602,388 immune cells, the same study demonstrated that these four consensus endotypes could be mapped onto two continuous axes of immune dysfunction: myeloid dysregulation and lymphoid dysregulation. This led to the development of the Hi-DEF (Human Immune Dysregulation Evaluation Framework), in which both axes are quantified as z-scores relative to healthy controls. A pathological threshold of $z \geq 1.65$ defines four quadrants: balanced, myeloid dysregulation, lymphoid dysregulation, and systemic dysregulation. Any form of dysregulation was associated with severe outcome, with an odds ratio of 5.2 (95% CI 3.9–7.0, $p < 2.2 \times 10^{-16}$), while systemic dysregulation was associated with an odds ratio of 7.1 (95% CI 5.6–8.9) [24].

The main distinction between Hi-DEF and earlier models lies in the transition from discrete categories to a continuous two-dimensional framework that incorporates clinical context, including infection type, disease severity, and age group. Importantly, the optimal thresholds for sensitivity and specificity varied according to both the diagnostic objective and the underlying type of infection [24].

3. Theranostics: endotype-specific treatment and heterogeneity of therapeutic effect.

Despite substantial progress in the standardization of sepsis management through the Surviving Sepsis Campaign, reductions in mortality have plateaued in high-resource

health-care settings. One major reason for this stagnation is that standardized treatment protocols continue to be applied to a biologically heterogeneous patient population [8, 26]. Retrospective analyses of completed randomized controlled trials consistently reveal heterogeneity of treatment effect (HTE), whereby the same intervention improves outcomes in one subphenotype while proving ineffective or even harmful in another (Table 3).

This principle is illustrated by several representative examples. In patients classified as SRS2, hydrocortisone increased 28-day mortality compared with placebo (OR 4.57; 95% CI 1.45–14.39; $p = 0.02$), whereas no such effect was observed in SRS1 [27]. Simvastatin reduced mortality only in the hyperinflammatory ARDS subphenotype, with no benefit in the hypoinflammatory group [28]. Activated protein C increased mortality in the hypoinflammatory phenotype but reduced it in the hyperinflammatory phenotype [29]. Similarly, convalescent plasma increased mortality in COVID-19 subphenotypes 2 and 3, while no harm was observed in subphenotype 1 [30].

Precision supportive care is an important complement to immunomodulatory strategies. The BLING III trial (2024) demonstrated the superiority of continuous over intermittent β -lactam infusion in sepsis [36]. The ADAPT-Sepsis study, published in JAMA in 2025, showed that biomarker-guided shortening of antibiotic therapy is both safe and effective [37]. Likewise, a 2025 study in the New England Journal of Medicine demonstrated that seven days of antibiotic therapy was non-inferior to fourteen days in patients with bacteremia, including those admitted to intensive care [38].

4. Dynamics of sepsis: temporal trajectories, epigenetics, and post-sepsis syndrome.

Although single-time-point analysis provides valuable diagnostic and prognostic information, it does not capture the evolving nature of sepsis [9]. One particularly informative dynamic marker is monocyte HLA-DR expression. In a real-world 20-year cohort of 1,023 patients with septic shock, Monneret et al. (2025) showed that early low mHLA-DR expression was less informative than the failure of

Table 3. Heterogeneity of therapeutic effect depending on sepsis subphenotype (selected examples)

Research	Syndrome	Subphenotypes	Intervention	Differential effect
Antcliffe, 2019 [27]	Sepsis	SRS1 (im.-suppressive) vs SRS2	Hydrocortisone	↑ mortality in SRS2 (OR 4.57)
Calfee, 2018 [28]	ARDS	Hyper- vs hypoinflammatory	Simvastatin	↓ mortality only in hyperinflammatory
Sinha, 2023 [29]	Sepsis	Hyper- vs hypoinflammatory	Activated protein C	↓ in hyperinflammatory; ↑ in hypoinflammatory
Bhatraju, 2019 [31]	Sepsis with ARDS	AKI-SP1 vs AKI-SP2	Vasopressin	↓ 90-day mortality in AKI-SP1
Fish, 2022 [30]	COVID-19	Subphenotypes 1, 2, 3	Convalescent plasma	Harm in subphenotypes 2 and 3

Note: HTE — heterogeneity of treatment effect; ARF — acute renal failure; OR — odds ratio.

its recovery between days 3 and 5, which independently predicted mortality [39]. These findings underscore the importance of longitudinal immune monitoring.

At the molecular level, transcriptomic alterations in sepsis are strongly influenced by reversible chromatin remodelling. Single-cell ATAC-seq has revealed changes in chromatin accessibility within myeloid precursors that stabilize a tolerant immune program [11]. These epigenetic alterations may persist well beyond the acute phase and are thought to contribute to both post-sepsis syndrome and Long COVID [9]. Up to 40% of sepsis survivors experience long-term physical, cognitive, and psychological sequelae [3]. Systems immunology has also revealed overlapping molecular mechanisms between post-sepsis syndrome and Long COVID, including persistence of the CR signature, expansion of myeloid-derived suppressor cells, and prolonged T-cell dysregulation [3, 7, 9].

5. Links with COVID-19 and implications for pandemic preparedness.

Systems immunology has revealed striking molecular similarities between severe COVID-19 and bacterial sepsis [5, 7]. After approximately one week in the intensive care unit, patients with severe SARS-CoV-2 infection and those with bacterial sepsis become nearly indistinguishable at the transcriptomic level [7]. Moreover, most endotypes identified in sepsis have also been reproduced in COVID-19 cohorts, including the inflammopathic/adaptive/coagulopathic framework [22]. Differential responses to corticosteroids across COVID-19 subphenotypes further parallel observations made in sepsis [30].

Technologies such as three-dimensional spatial transcriptomics, including SHM-seq and SmT, now allow direct mapping of both host and pathogen transcripts within tissue architecture, including FFPE lung sections from patients with

COVID-19 [11]. These developments suggest that systems immunology could evolve into a pathogen-agnostic platform for future pandemic preparedness. However, achieving this goal will require sustained international collaboration and targeted funding [9, 42].

6. New horizons: targeted immunotherapy and adaptive platform trials.

Accumulating evidence suggests that specific immunomodulatory agents may benefit selected sepsis subphenotypes. Recombinant human IL-7 has been shown to enhance CD4⁺ lymphocyte proliferation and IFN- γ production and may therefore be particularly relevant in SRS1/NPS-like states characterized by lymphocyte depletion [43]. GM-CSF has been reported to restore monocyte function in patients with features of immunoparalysis [39]. Anakinra, an IL-1 receptor antagonist, achieved a 42.9% 7-day survival rate in a cohort with features of macrophage activation syndrome [43]. Nevertheless, these findings are derived primarily from small pilot studies and still require prospective validation.

In this context, the conventional randomized controlled trial design, based on a single intervention versus control, appears increasingly inadequate for a syndrome as heterogeneous as sepsis. Adaptive platform trials, including PANTHER, TRAITS, and Immunosept [26, 42], offer a more suitable framework by allowing the simultaneous evaluation of multiple agents, dynamic modification of enrollment according to endotype, and prospective testing of endotype-specific efficacy. Such designs may prove essential for overcoming the current therapeutic ceiling in sepsis care.

Discussion

1. Systems immunology: methodological foundations and analytical tools.

Table 4. Summary comparative analysis: Hancock et al. 2024 vs. Contemporary Science 2024–2025

Aspect	Hancock et al., 2024 [9]	Current research, 2024–2025	Key sources
Endotypes	5 discrete (NPS, INF, IFN, ADA, IHD)	4 consensus + two-dimensional Hi-DEF continuum	Moore et al., 2025 [24]
Technology	Bulk RNA-Seq + ML	scRNA-seq, scATAC-seq, CITE-seq, 3D spatial transcriptomics	Yang et al., 2025 [11]
Clinical translation	Potential endotype-specific tests	FDA-authorised AI test; portable bedside test (UBC)	Bhargava et al., 2024; Malic et al., 2025 [17, 18]
Logic of endotypes	Descriptive clustering	Causal inference, ‘treatable traits’	Baillie et al., 2024 [12]
Pathogenesis	Predominantly immune dysregulation	Triad: immune + endothelial + coagulation dysfunction	Girardis et al., 2024 [40]
Dynamics	Longitudinal analysis as a prospect	mHLA-DR trajectory: critical; 30% change endotype within 48 hours	Monneret et al., 2025 [39]; Antcliffe et al., 2025 [26]
Microbiome	Not considered	Intestinal dysbiosis — key factor in severity	Klingensmith et al., 2025 [41]
Global accessibility	Not considered	85% of deaths in LMIC; consensus for limited resources	Thwaites et al., 2025 [25]
Note: LMIC — low- and middle-income countries; mHLA-DR — expression of the HLA-DR molecule on monocytes.			

Systems immunology is a branch of systems biology that applies computational and mathematical approaches to the analysis and modelling of the immune system as a complex, integrated biological network [9]. Its clinical relevance lies in the fact that disease states are not interpreted through isolated biomarkers, but through the coordinated behaviour of interdependent components. In humans, approximately 5,000 of the roughly 11,000 expressed genes are thought to participate in immune regulation, forming extensive interaction networks that extend beyond the immune system itself and involve the endocrine, nervous, cardiovascular, and other physiological systems [9].

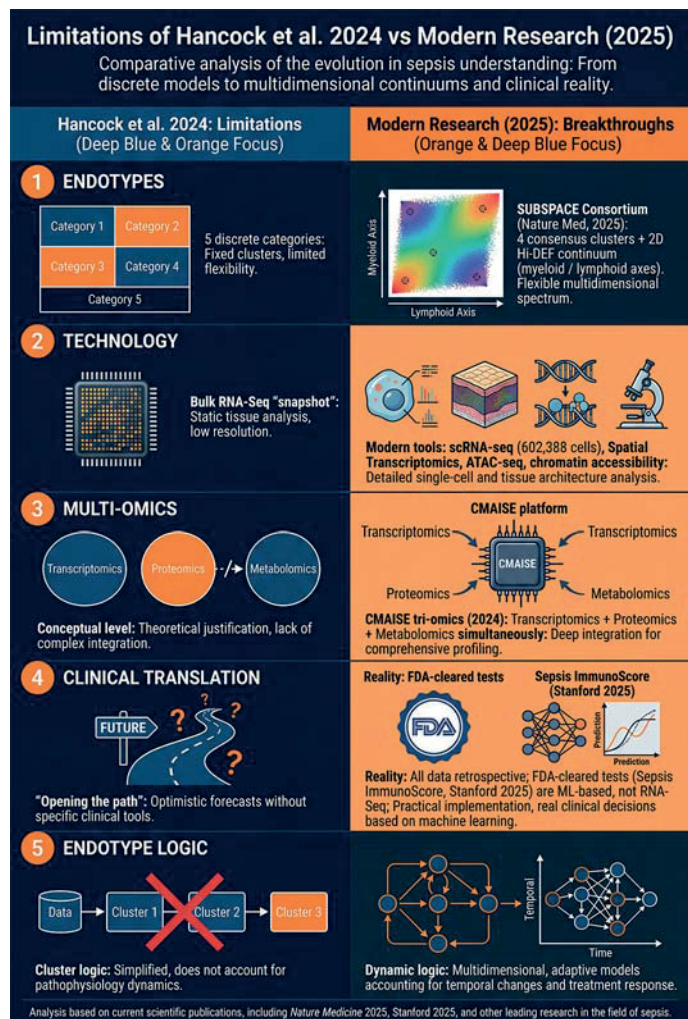
The methodological foundation of systems immunology includes several complementary approaches. Transcriptomics, particularly RNA-Seq, remains the most widely used method for obtaining genome-wide data in real time. Machine-learning methods are used to detect hidden structure within these data and include both supervised approaches, such as neural networks, decision trees, and support vector machines, and unsupervised approaches, such as hierarchical clustering and k-medoids. Network biology provides tools for analyzing protein-protein interaction networks, often using platforms such as NetworkAnalyst and Cytoscape. Finally, multi-omic integration combines genomics, transcriptomics, proteomics, metabolomics, lipidomics, and microbiomics to generate a more comprehensive representation of host biology [9, 10].

Recent technological advances have considerably expanded this toolkit. Single-cell RNA sequencing enables the characterization of gene-expression programs at the level of individual immune cells; single-cell ATAC-seq captures chromatin accessibility at single-cell resolution; and three-dimensional spatial transcriptomics maps immune programs within intact tissue architecture [11]. At the same time, the field is undergoing an important methodological transition from descriptive clustering toward causal inference, to identify mechanistic pathways and “treatable traits” that can be targeted therapeutically [12].

2. Critical appraisal of the Hancock et al. (2024) framework.

Despite the major conceptual contribution of Hancock et al. (2024) [9], comparison with evidence published in 2024–2025 reveals several important limitations. These differences are summarized in Table 4 and illustrated in the Figure.

First, the concept of discrete endotypes may oversimplify the biological reality of sepsis. The five-category model proposed by Hancock and colleagues (NPS, INF, IFN, ADA, and IHD) does not fully capture the continuum of immune dysregulation observed in contemporary datasets. In contrast, the Hi-DEF framework proposed by Moore et al. (2025) offers a two-dimensional continuous representation that appears to be both conceptually and clinically more robust [24]. Notably,



A comparative analysis of studies by Hancock et al. (2024) with new studies from 2025

the optimal number and boundaries of clusters depend on context, including disease severity and infection aetiology.

Second, the technological basis of the Hancock model is now limited by comparison with more recent approaches. Bulk RNA-Seq averages gene expression across mixed cell populations and may therefore obscure clinically meaningful heterogeneity [11]. By contrast, scRNA-seq, scATAC-seq, CITE-seq, and three-dimensional spatial transcriptomics allow cell-resolved profiling, tissue-level reconstruction, and in situ analysis of host-pathogen interactions [11].

Third, Hancock et al. primarily present multi-omics as a future direction rather than an integrated analytical standard. More recent studies have already identified metabolic subphenotypes associated with lysophospholipid signatures and endothelial activation [26], and trimodal integration of transcriptomics, proteomics, and metabolomics has been demonstrated in the Chinese CMAISE database (2024). This broader molecular perspective is likely to be necessary for clinically meaningful stratification.

Fourth, essentially all current associations between endotypes and treatment response remain retrospective. To date, no completed prospective randomized trial has definitively confirmed the benefit of endotype-guided therapy [26]. Ongoing adaptive platform studies, such as PANTHER, TRAITS, and Immunosept, will therefore be critical for determining whether biological stratification can improve outcomes in practice [26].

Fifth, the pathogenetic framework itself has broadened. Girardis et al. (2024) proposed that sepsis should be understood not only as immune dysregulation, but as the simultaneous failure of three interrelated systems: immunity, endothelium, and coagulation [40]. This triadic model helps explain why immunologically focused strategies may have limited success when endothelial injury and coagulopathy remain unresolved.

Sixth, the methodological logic of endotyping remains predominantly descriptive. As argued by Baillie et al. (2024), cluster-defined endotypes do not necessarily identify mechanisms; rather, they classify patterns [12]. A shift toward causal inference is therefore needed if the field is to move from association-based stratification to genuinely mechanism-driven therapeutic targeting.

Seventh, the microbiome remains underrepresented in the Hancock framework. Yet emerging evidence suggests that gut dysbiosis may play a central role in amplifying systemic inflammation and influencing disease severity, while also representing a potential therapeutic target through approaches such as probiotics or faecal microbiota transplantation [41].

Finally, the issue of global inequity cannot be ignored. Approximately 85% of sepsis cases and deaths occur in low- and middle-income countries [2, 25], where transcriptomic diagnostics costing \$500–1000 per sample are unlikely to be scalable. In this respect, the international LMIC-focused consensus proposed by Thwaites et al. (2025) represents an important corrective step [25].

3. Interpretation, clinical implications, and future directions.

Taken together, the evidence shows that systems immunology has fundamentally reshaped the understanding of sepsis, transforming it from a monolithic syndrome into a biologically heterogeneous set of endotypes. Hancock et al. (2024) [9] articulated the core principles of this shift, namely the movement away from uniform treatment protocols and toward biologically informed, endotype-specific strategies. The most important advance of 2025 was the validation of consensus endotypes by the SUBSPACE consortium [24], which for the first time demonstrated the reproducibility of major endotypic structures in a large independent population of 3,380 patients across 12 cohorts and 10 centres. More broadly, the contrast between the

Hancock model and the current state of the field is summarized in *Table 4*.

Clinical translation, however, remains the central challenge. AI-based diagnostic tools have already achieved accuracies above 90% without relying on RNA-Seq [17, 18], but they do not provide the mechanistic resolution needed to guide precision immunotherapy. A pragmatic future strategy may therefore involve a stepwise diagnostic model in which rapid, low-cost AI screening is followed by deeper endotypic profiling in high-risk patients.

The pathogenetic triad proposed by Girardis et al. [40] further strengthens the systems framework by highlighting why restoration of immune function alone may be insufficient in the absence of correction of endothelial dysfunction and coagulopathy. In parallel, the transition from a mean arterial pressure-centred to a perfusion-centred approach in resuscitation reflects a broader conceptual shift in the management of septic patients [35].

Several methodological issues also remain unresolved. All current HTE analyses are retrospective [26], and dynamic instability further complicates interpretation: approximately 30% of patients may change metabolic subphenotype within 48 hours. In addition, the effects of comorbidities, previous therapy, and treatment timing must be incorporated into future models. Standardization of analytical pipelines for scRNA-seq and spatial transcriptomics is another priority if reproducibility across centres is to be achieved [11].

The issue of global accessibility may ultimately be the most pressing. Most advanced endotyping strategies have been developed and validated in highly specialized centres in the United States, the United Kingdom, and the Netherlands, whereas the overwhelming burden of sepsis mortality falls on resource-limited settings [2, 25]. The GSA/Thwaites 2025 consensus is an important beginning, but true implementation will require deliberate adaptation of these technologies to the realities of low-resource care environments.

Conclusions

1. Systems immunology is shaping a new paradigm for the management of sepsis, moving from a 'universal bundle' of treatments to more precise, endotype-specific strategies for diagnosis and treatment.

2. Five molecular endotypes (NPS, INF, IFN, ADA, IHD) and the consensus two-dimensional Hi-DEF framework (2025, $n=3380$, OR of systemic dysregulation=7.1) have been demonstrated to demonstrate different mechanisms of immune dysfunction and potential response to therapy.

3. Retrospective RCT analyses (covering over 10 studies) have demonstrated the efficacy of HTE, indicating that the same therapeutic intervention can yield divergent outcomes, depending on the specific subphenotype. This finding underscores the necessity for endotype-oriented research, which

aims to tailor therapeutic interventions to the distinct characteristics of individual endotypes.

4. The utilisation of AI–authorised bedside tools (FDA 2024; UBC 2025) and novel transcriptomic signatures has been demonstrated to achieve a diagnostic accuracy of over 90% in the identification of patients at risk of sepsis (Smith et al., 2024).

5. The concept of the pathogenetic triad (immune + endothelial + coagulation dysfunction) and the methodology of causal inference represent significant conceptual contributions to the systemic immunological framework.

6. Future research should prioritise the following: the execution of prospective adaptive platform randomised controlled trials (RCTs) based on endotypes; the standardisation of single–cell RNA sequencing (scRNA–seq) and spatial transcriptomics analytical methods; and the guaranteeing of global accessibility of precision approaches for low– and middle–income countries (LMICs).

Conflict of interest. The authors declare that there is no conflict of interest regarding the materials published in this article.

Ethical approval statement. The article is a review of the literature and did not require a separate decision by the bioethics committee. All original studies cited were conducted in accordance with international standards for biomedical research involving human subjects (Helsinki Declaration).

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