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Genetic, Metabolic, and Proteomic Polymorphisms and Clinical Phenotypes of Sepsis

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Summary

The heterogeneity of sepsis patient populations remains an unresolved issue, hindering the development of effective therapeutic strategies and disease prognostic tools. Classification of diverse sepsis patients by molecular endotypes, together with multi-omics profiling, enables a more personalized treatment approach. Studying the immune response, genomic, metabolomic and proteomic profiles of sepsis patients will enable clinical phenotyping of this diverse population and the development of a precision approach to the diagnosis, prognosis and treatment of sepsis and septic shock.

The aim of the review was to discuss sepsis subtypes as identified by profiling of patient genomic, metabolic, and proteomic data and present the latest approaches addressing the heterogeneity of sepsis patient populations, such as multi-omics endotyping and clinical phenotyping, which may aid in targeted therapy and optimization of diagnosis and therapy. The keywords «sepsis omics», «sepsis endotypes», and «sepsis heterogeneity» were used to search PubMed databases without language restrictions. From over 300 sources, 120 were selected for analysis as being most relevant to the aim of the review. More than half of these were published within the last five years. Criteria for excluding sources were their inconsistency with the aims of the review and their low informativeness.

This review discusses the different types of immune responses, the impact of patient population heterogeneity on therapeutic interventions, and current perspectives on phenotyping sepsis patients. Despite the limitations of centralized collection of clinical information, cluster analysis of large data sets and the role of immune response genomics, metabolomics, and proteomics are beginning to dominate the prognosis and treatment of sepsis. Establishing links between all these elements and attempting clinical phenotyping of sepsis, including subtype analysis, appear to be critical in the search for personalized treatment approaches in the near future.

Conclusion. Currently, the widely accepted goal in sepsis management is early detection and initiation of therapy to prevent the development of irreversible septic shock and multiorgan failure syndrome. Personalized genetic, metabolomic and proteomic profiling of the patient seems to be an intriguing and promising avenue in the search for new treatment strategies in sepsis.

Keywords: sepsis; omics studies, genomics of the immune response; metabolomics of the immune response; proteomics of the immune response; phenotypes of sepsis

Conflict of interest. The authors declare no conflict of interest.

Introduction

Sepsis does not progress or manifest in the same way in all patients due to the marked heterogeneity of septic patients and differences in pathophysiological and immunological responses.

Heterogeneity is a major feature of the sepsis patient population, and if one can stratify them into distinct groups (phenotypes), the latter will differ not only in pathophysiological patterns but also in responses to therapy.

Specific characteristics such as sex, age, race, comorbidities, smoking, alcohol consumption, medications, obesity, and nutritional status, as well as the source of infection, the type of infectious agent, the treatment administered, the nature of the underlying disease, and the conditions that cause immune dysfunction (liver cirrhosis, cancer, and autoimmune diseases) are obvious, but not exclusive, reasons for patient heterogeneity. Individual variability in the nature of the immune and pathophysiological response accounts for the wide range of clinical variants of sepsis.

Patients with sepsis were dying in the mid-twentieth century, despite the discovery of penicillin and the absence of antibiotic resistance problems as we know them today. Numerous disparate ob-

servations from those years led an increasing number of researchers to conclude that the root of the problem was not only the pathogen itself, but also (perhaps to a greater extent) the patient's inflammatory response, consistent with Osler's views. In the years that followed, this view of the pathophysiology of sepsis became dominant.

Sepsis was defined in 1992 as a clinical syndrome that included both infection and systemic inflammatory response syndrome (SIRS) as measured by temperature, heart rate, respiratory rate, and leukocytosis [1]. These criteria were so broad that almost any patient with an acute respiratory viral infection or, for example, pancreatitis met the definition of sepsis. However, it was the high mortality rate from sepsis during those years that forced the scientific community to act in this way, allowing any intensivist to suspect sepsis before the onset of septic shock and make an early clinical diagnosis. However, the low specificity of the SIRS diagnostic criteria resulted in an extremely large population of patients meeting the diagnostic criteria for sepsis, posing significant challenges in both clinical practice and research.

In 2001, the updated definition of sepsis was published, which was almost identical to the previous one; it simply expanded the list of sepsis criteria [2]. Despite the introduction of another definition in 2016, which emphasized that sepsis is a life-threatening organ dysfunction caused by an unregulated host response to infection [3], it remains very difficult to describe this response in detail because we lack the tools to objectively assess whether a given organism's response to infection is normally regulated or not. Because immune responses are unique, answering the question «What should be considered immune dysfunction?» can be challenging. Indeed, in this context, heterogeneity becomes a hallmark of sepsis [4].

As a result, future studies of the efficacy of different therapeutic interventions in sepsis should use endo- and phenotyping to stratify sepsis patients in clinical trials and to develop treatment strategies that are more precisely targeted to specific endo- and phenotypes of sepsis.

The primary objective of this review is to familiarize the reader with the stratification of different endotypes obtained using omics technologies (genomic, transcriptomic, proteomic, metabolomic, etc.) as well as the phenotyping of sepsis patients using large clinical datasets.

The literature search was performed in the bibliographic database PubMed without language restrictions. The keywords «sepsis omics», «sepsis endotypes», and «sepsis heterogeneity» were used in the search queries to link the topics of omics research and sepsis phenotyping. The analysis included 120 sources that were most relevant to the main objective of the review.

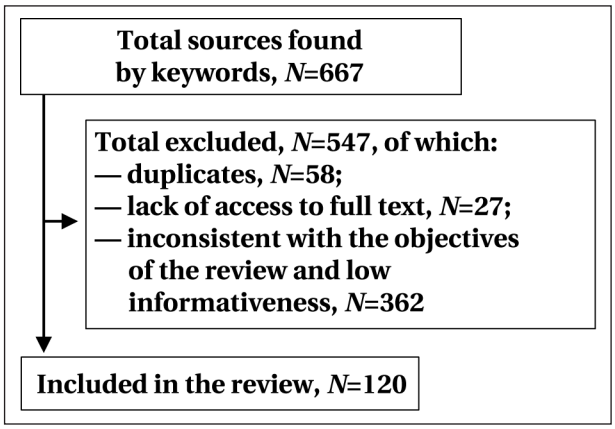

Fig. 1. Flow chart for searching and selecting papers for inclusion in the review.

Criteria for excluding sources were irrelevance to the review objective and low informativeness. The current review included 6 comparative studies, 3 prospective cohort studies, 17 observational studies, 51 original studies, 6 commentaries, 20 reviews, 1 meta-analysis, and results from 16 clinical trials. The source selection scheme is shown in Fig. 1.

Genomics of the sepsis-related immune response. Individual transcriptome variations during sepsis have been evaluated by various authors in several large cohorts based on a dysfunctional (immunosuppressive) endotype of the immune response to sepsis. Data from clinical and laboratory studies included peripheral blood leukocyte counts obtained within the first hours of admission to the intensive care unit in patients with probable infection. These studies used an unsupervised hierarchical clustering method for approximately 25,000 transcriptomic profiles across the genome (gene expression microarray and RNA sequencing). These complex methods, based on large amounts of genetic data, have enabled the identification of patterns among expressed genes that define molecular subgroups representing different abnormal conditions that are not necessarily associated with specific clinical outcomes, but may be related to them. This approach can also identify clusters based on a patient's premorbid status (age, comorbidities), stage and severity of disease, likelihood of mortality, and genetic predisposition to severe sepsis.

One of the first studies to use unsupervised hierarchical clustering to investigate subgroups of sepsis patients in the general ICU population was conducted in a cohort of children admitted with septic shock to pediatric ICUs in the United States [5]. The attempt by Wong et al. to develop a clinically feasible personalized medicine approach to pediatric septic shock resulted in the first genetic profiling of a heterogeneous group of septic shock patients. According to differential patterns of full genomic expression, 2 subclasses were defined using a spe-

cially developed gene expression parameter. This method of patient categorization was prospectively analyzed in a separate cohort of patients: out of 132 patients, 63 patients were classified as endotype A and 69 patients as endotype B. Initially, these two subclasses differed in age and leukocyte count distribution: patients with endotype A were significantly younger (mean age 1.4 years vs. 4.1 years for subclass B), and endotype A had a lower total leukocyte and neutrophil count than endotype B. The clinical phenotypes of the subtypes also differed: endotype A had a significantly higher 28-day mortality in the ICU (11% vs. 4% for endotype B), and endotype A had a more complicated course (27% vs. 11%) [5]. In a previous study by the same authors using the same patient sample, patients in the endotype A group showed the greatest disruption of immune defense pathways, specifically the suppression of key genes essential for the adaptive immune system, including those involved in glucocorticoid receptor pathways [6].

In 2016, an updated perspective of leading intensive care specialists on the phenomenon of immune dysregulation in sepsis was published [7]. Davenport et al. performed a transcriptomic analysis of peripheral blood leukocytes from patients admitted to the intensive care unit. Transcriptomic profiles of 265 patients admitted to 29 ICUs in the UK as part of the Genomic Advances in Sepsis (GAinS) study demonstrated two endotypes of the immune response to sepsis: SRS1 (41%) and SRS2 (59%) [8]. Patients with the SRS1 endotype had a higher 14-day mortality rate than those with the SRS2 endotype (22% vs. 10%). SRS1 was also associated with relative immunosuppression, endotoxin tolerance, T-cell depletion, HLA class II suppression, and metabolic disturbances (shift from oxidative phosphorylation to glycolysis). Only seven of the more than 3000 differentially expressed genes accurately predicted classification into a specific SRS endotype. The Davenport research group hypothesized that in future studies, patients with a prospectively defined SRS1 endotype might benefit from therapy that increases the pro-inflammatory response in sepsis. The same investigators later replicated this analytical approach to examine gene expression patterns in 117 patients with fecal peritonitis (FP) [9]. Again, two distinct groups were identified: SRS1(FP) — 46% and SRS2(FP) — 54%, with patients in the SRS1(FP) group having a higher 14-day mortality rate (19% vs. 4%). The results were consistent with those found in the previous study, which included patients with sepsis caused by community-acquired pneumonia [8], indicating an increased tolerance to LPS in the SRS1(FP) patient group. A simpler set (this time consisting of 6 genes) was obtained from over 1000 expressed genes that predicted classification into a particular SRS endotype. It should be noted that the patterns of SRS gene expression that distinguish the «immunosuppressive» SRS1/SRS1(FP) endotype in adults did not correspond to the similar endotype A in children [5].

Several other studies have shown that more than 80% of the transcriptomic response in sepsis is independent of the source or pathogen of the primary infection [9,10]. Furthermore, these patterns are similar to those observed in patients with trauma or burns [11], as well as in critically ill patients with non-infectious respiratory distress syndrome [12].

In a prospective observational cohort study of 306 patients admitted to two intensive care units in the Netherlands between January 1, 2011, and July 20, 2012, as part of the Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project (discovery and first validation cohorts), and patients hospitalized with sepsis due to community-acquired pneumonia in 29 intensive care units in the United Kingdom (second validation cohort), whole-genome blood gene expression profiles were generated from samples collected on admission [13]. The obtained data were analyzed using unsupervised consensus clustering and machine learning software. Four molecular endotypes were found to be associated with 28-day mortality ($P = 0.022$): on day 28, mortality was highest in the Mars1 group (39%), followed by 22% in the Mars2 group, 23% in the Mars3 group, and 33% in the Mars4 group [13].

The Mars1 endotype showed decreased expression of genes related to key innate and adaptive immune cell functions, including Toll-like receptors, NFκB1 signaling, antigen presentation, and T cell receptor signaling. However, an increased expression of trigger genes for specific metabolic pathways, including heme biosynthesis was seen in this endotype. The Mars2 endotype showed increased expression of genes related to pattern recognition, cytokine signaling, cell growth, and motility, such as NF-κB, IL-6, inducible nitric oxide synthase, and N-formylmethionyl peptide signaling. The Mars4 endotype was also associated with increased expression of genes involved in pattern recognition and cytokine interactions, specifically interferon signaling, RIG1-like receptors, and TREM1 signaling. The Mars3 endotype was primarily associated with increased expression of genes in the adaptive immune pathway, such as T helper cells, NK cells, IL-4 signaling, and B cells. The combinations of the AHNAK and PDCD10 genes were selected as biomarkers for this endotype [13]. To facilitate potential clinical use, for each endotype, specific biomarkers were used: BPGM and TAP2 reliably identified patients with the Mars1 endotype, GADD45A and PCGF5 with Mars2, and IFIT5 and GLTSCR2 with Mars4 [13]. The primary aim of our study was to identify sepsis endotypes and compare their clinical signs and survival outcomes. The study also identified

candidate biomarkers for further identification of specific sepsis endotypes in clinical practice [13].

Recent cost reductions in whole exome sequencing (WES) technologies have made genomic research more accessible. In one such study, researchers hypothesized that certain variations in specific genes involved in the pathogenesis of syndromes such as macrophage activation syndrome (MAS) and atypical hemolytic uremic syndrome (aHUS) would be more common in sepsis patients, resulting in marked inflammation. The researchers used ferritin levels above 7000 ng/ml as a screening marker and performed WES in six patients [14]. All patients inherited at least one abnormal (or likely abnormal) genomic variant previously identified in the literature as a cause of hereditary immunologic diseases. For example, three of six patients had the UNC13D variant, which causes abnormal natural killer (NK) cell degranulation and altered cytolytic activity. The autosomal recessive inheritance of this variant results in familial hemophagocytic lymphohistiocytosis type 3. Three patients had a series of aHUS-associated mutations in complement pathway genes, including two in the CD46 gene, one in C3, and one in CFHR5, all of which were associated with nucleotide substitutions [14].

There are distinct patterns of gene expression among granulocyte and lymphocyte subpopulations, reflecting the specialized function of each immune cell [15]. Because the transcriptome profile varies between immunocompetent cell types, gene expression patterns may reflect different leukocyte populations rather than intracellular differences in gene expression. These findings also need to be validated in larger cohorts from different countries, as ethnic background is a strong predictor of gene expression [16].

Currently, ncRNAs (non-coding RNAs) and miRNAs (microRNAs) are being investigated for their prognostic value in sepsis. A non-coding RNA molecule is one that is transcribed from DNA but not translated into proteins. miR is a small non-coding RNA molecule that regulates post-transcriptional gene expression. Huang et al. found that lncMALAT1 (long non-coding transcript 1 associated with lung adenocarcinoma metastasis) and miR-125a were elevated in septic patients compared to healthy controls, while in non-survivors they were positively correlated with APACHE II and SOFA scores and serum creatinine levels [17,18].

V. M. Pisarev et al. found that increased plasma levels of extracellular DNA (ecDNA) were associated with 30-day mortality in sepsis patients [19]. In turn, ecDNA acts as a ligand for one of the toll-like receptors (TLR9). Patients with the TLR9 CC genotype had the highest levels of cfDNA compared to other genotypes. The C allele of the TLR9 genetic variant (s352162) has been associated with multiple organ failure and increased TNF-α production [19,20]. The simultaneous use of markers such as cfDNA and the genetic marker TLR9 most accurately predicts the fatal outcome of ICU patients [19]. Thus, in the future, targeted therapy using TLR9 receptor inhibitors could be developed as one of the personalized treatment approaches.

In 2020, the results of a Russian prospective study on the prognostic potential of aquaporin AQP5 as a biomarker for the course and outcome of sepsis were published [21]. Among all ICU patients, the homozygous AA variant of AQP5 genotype was most frequent. Sepsis patients with AQP5 AC and CC genotypes had a higher survival rate than those with the AA variant. In non-abdominal sepsis, however, mortality was not affected by single nucleotide substitution (AQP5). Only in patients with abdominal sepsis was there a significant difference in survival between genotypes: patients with the AQP5 AA genotype had higher mortality than patients with the AC and CC genotypes. The authors concluded that the C allele predicts a better outcome in abdominal sepsis [21]. The results of another Russian study on the relationship between sepsis severity and the prognostic significance of the aquaporin 4 (AQP4) genetic variant were published in 2023 [22]. The study included patients from three intensive care units. The majority of patients carried the GG AQP4 genetic variant, while homozygous carriers of the minor T allele were rare. The frequency of septic shock was significantly lower in patients with the GT and TT genetic variants than in patients with the GG genotype [22]. Interestingly, when the frequency of septic shock was compared between patients in different ICUs, it was found that the protective effect of the T allele was not statistically significant for patients in ICU-1, contrary to the patients in ICU-2 and ICU-3 who had a higher frequency of comorbidities and a higher SOFA score on admission [22]. Thus, the presence of the T allele in the 3' region of the AQP4 gene had a protective effect only in patients with severe multiple organ failure and comorbidities and was associated with a better course of sepsis in these patients.

In 2021, a Russian study was conducted to evaluate the contribution of the angiotensin II receptor 1 gene (AGTR1) polymorphism to outcomes in patients with sepsis and various comorbidities [23]. In the patient cohort studied, CIRS and Charlson Scale scores were significantly associated with sepsis mortality. Among all patients, homozygotes with the TT AGTR1 genotype dominated, while homozygotes with the AA AGTR1 genotype had the lowest frequency.

There were no significant differences in comorbidity between patients with different AGTR1 genotypes. No significant differences in mortality rates between the different AGTR1 variants were

found; however, patients with the TT genotype had a lower incidence of septic shock. In patients with cardiovascular comorbidities, carriers of the TA and AA variants had a higher mortality rate (16 of 16 cases) than carriers of the TT variant (25 of 33 cases) [23]. The TA and AA variants also had a higher risk of developing septic shock. The presence of the AGTR1 genotype determined the severity and outcome of sepsis in patients with type 2 diabetes: mortality was significantly lower with the TT variant compared to the TA and AA variants. When patients with severe cardiovascular disease and diabetes mellitus were combined into a single group, the mortality rate among carriers of the TT genetic variant was 69%, while carriers of the A allele had a mortality rate of 96% [23]. The association of the AGTR1 polymorphism with disease progression and outcome in septic ICU patients with severe comorbidities may become an important prognostic indicator in the future.

The presented studies provide evidence for the existence of distinct categories of the body's immune response to infection in the context of sepsis and potential therapeutic targets, with a differential approach to interpreting the clinical picture of sepsis based on the expressed molecular pathways that distinguish immune response endotypes in different patients [5, 8, 13, 15, 16, 24]. Furthermore, each of the cited studies proposed a potential «dimensionality reduction» of the multidimensional data from whole genome expression analysis into manageable prognostic clusters that could be incorporated into a simpler test applicable at the point of care, thereby facilitating the translation of the presented basic research results into real clinical practice.

Metabolomics of the immune response in sepsis. Epigenetic regulation of gene function has been identified as a key mechanism controlling myeloid cell function in sepsis patients. Transcriptional regulation involves the organization of gene loci on chromatin into transcriptionally active or «silent» states [25]. Transcriptionally active euchromatin is accessible to transcription factors and polymerases, whereas transcriptionally «silent» heterochromatin is inaccessible and inhibits gene transcription. Histone modifications such as acetylation, methylation, ubiquitination and phosphorylation all affect chromatin activation. Thus, various cellular metabolites serve as cofactors for epigenetic enzymes that induce chromatin and DNA modifications, modulate gene transcription, and promote different functional programs in sepsis: immunoparalysis or excessive inflammation [26–29]. A specific example of such epigenetic regulation is the Warburg effect, a shift from oxidative phosphorylation to glycolysis that leads to succinate accumulation, which in turn is critical for increasing the stability of hypoxia-inducible factor 1α (HIF1α), a transcription factor that increases IL1b transcription (which encodes IL-1β) [27].

Finally, in addition to the immune, genetic, and cellular regulatory pathways discussed above, a variety of other mechanisms influence the overall inflammatory response system in sepsis. These include neuroinflammation (which involves transmission of a peripheral sensory signal via the afferent vagus nerve to the brainstem, stimulation of the efferent vagus nerve, and subsequent activation of the splenic nerve in the celiac plexus, which leads to the release of norepinephrine in the spleen and the secretion of acetylcholine by a subpopulation of CD4+ T lymphocytes [30] with acetylcholine inhibiting the release of proinflammatory cytokines by macrophages) and a shift in the acid-base balance of the internal environment towards acidosis [31].

Several studies have investigated the metabolomic profiles of patients with sepsis. Schmerler et al. used targeted metabolomics to identify molecules that distinguish sepsis from non-infectious SIRS. They used liquid chromatography-mass spectrometry (LC-MS) to analyze 186 metabolites found in 74 SIRS patients and 69 sepsis patients, including acylcarnitine, amino acids, biogenic amines, glycerophospholipids, sphingolipids, and carbohydrates. In this study, acylcarnitine and glycerophospholipid activities were found to be significantly different in patients with sepsis compared to SIRS. Using these two markers, the researchers correctly identified SIRS and sepsis in 80% of patients [32].

Another study found metabolic differences between healthy individuals, patients with SIRS, and patients with sepsis. Patients with sepsis had significantly lower concentrations of lactitol dehydrate and S-phenyl-D-cysteine, but higher concentrations of S-(3-methylbutanoyl)dihydrolipoamide E and N-nonanoylglycine than patients with SIRS. This study also found that 2-phenylacetamide, dimethyllysine, glyceryl phosphoryl ethanolamine, and D-cysteine were associated with the severity of sepsis. In addition, the profiles of sepsis patients 48 hours before death showed a clear state of metabolic derangement, with levels of metabolites such as S-(3-methylbutanoyl)dihydrolipoamide E, phosphatidylglycerol, glycerophosphocholine, and S-succinylglutathione significantly reduced ($P < 0.05$) [33].

The gut microbiota deserves special attention because it is thought to influence systemic immune responses by translocating microbial components from the gut into the bloodstream. The research of N.V. Beloborodova et al. contributes to our understanding of the role of the intestinal microbiota in normal and pathological conditions, including sepsis [34-37]. There are several microbial metabolites that may influence the body's response to infection in sepsis. For example, hydroxylated aromatic mi-

crobial metabolites have been found to dominate the metabolic profile of serum phenolic metabolites in sepsis patients. These metabolites may affect neutrophil function by suppressing their activity, which may contribute significantly to the development of immunosuppression.

The regulatory mechanisms described above are not only the result of genetic and cellular regulation of immune system responses to infectious agents (based on individual characteristics), but also of factors that can have a significant impact on these responses.

Proteomics of the immune response in sepsis. Biological profiling of sepsis patients is based on the measurement of proteins in various biological samples, which is more widely accepted and feasible than genetic or metabolomic profiling. Each method for testing a biological sample has advantages and disadvantages. Plasma and serum samples are the most readily available for clinical evaluation. As a result, a considerable amount of information has already been gathered from studies that have attempted to classify sepsis using their analysis [38–50].

One notable method that may provide a new way to categorize a heterogeneous group of septic patients is the use of molecular and protein biomarkers to predict outcome in septic shock patients. This approach has been used to stratify the risk of pediatric septic shock using a previously validated risk score consisting of 5 plasma protein biomarkers (PERSevere) [40] and their combination with 4 genes, including DDIT4, HAL, PRC1, and ZWINT, which are directly linked to TP53 and are likely to be associated with adverse outcomes [41]. Parameters used to assess 28-day mortality risk showed improved prediction ability. Plasma biomarkers were associated with dysfunctional inflammation and cellular damage, while genes were associated with the p53 protein, a transcription factor that acts as a tumor suppressor: activated when DNA damage accumulates, it causes the cell cycle arrest or induces apoptosis when cells are irreversibly damaged.

The first proteomic analysis of serum from sepsis and septic shock patients was performed by A. Kalenka et al. [42]. This study compared the proteomic profiles of survivors and non-survivors with the goal of identifying early differences in serum composition that might predict survival at day 28. Several differentially expressed proteins were identified, including complement factor Bb, α-1-B-glycoprotein, and clusterin [42]. The Bb segment of factor B, a component of the alternative complement pathway, plays a key role in the body's initial defense against infection. Factor B is essential for the activation of this pathway, serves as a cofactor in antibody-dependent monocyte-mediated cytotoxicity, and enhances macrophage adhesion and plasminogen activation [51, 52]. The study found higher activity of these proteins in survivors compared to non-survivors. Meanwhile, α-1-B-glycoprotein — a member of the immunoglobulin superfamily and a well-known plasma protein with an unclear biological function — was elevated to a greater extent in non-survivors. Haptoglobin, an acute-phase protein with molecular heterogeneity resulting from genetic polymorphism, is elevated during inflammation, infection, and cancer, making it a biomarker for several diseases [53, 54]. There are two common haptoglobin alleles, Hp1 and Hp2. Homozygous individuals for these alleles express Hp 1-1 and Hp 2-2, respectively, whereas heterozygotes express Hp 2-1 [55]. Notably, Hp 1-1 has greater antioxidant activity compared to Hp 2-2 [56]. One study investigated the effects of haptoglobin isolated from healthy individuals with the Hp 1-1 phenotype on cytokine production by lipopolysaccharide (LPS)-stimulated monocytes. In vitro results showed that haptoglobin inhibited the release of TNF-α, IL-10 and IL-12 from LPS-stimulated human monocytes, but did not significantly affect IL-6 or IL-8 levels. In vivo models further confirmed the potent anti-endotoxic properties of haptoglobin. The authors suggested that haptoglobin acts as a selective modulator of inflammation by preventing excessive production of proinflammatory cytokines. In particular, inhibition of IL-12 release was proposed to promote a T helper type 2-dominant environment. Because of its anti-endotoxic effects, haptoglobin is considered a potential therapeutic agent for inflammation [57]. Sepsis survivors showed a more pronounced upregulation of haptoglobin, possibly reflecting a stronger immune response. Clusterin activity was also increased in survivors, with expression dependent on specific factors (26.5 and 14.9) [42]. Clusterin is thought to play a role in the clearance of toxic substances through its ability to bind unfolded proteins, cellular debris, and immune complexes [58].

In a prospective observational study, M. S. Raju et al. analyzed changes in the serum proteome from early to late stages of sepsis in survivors compared to non-survivors [43]. The study identified differences in the levels of several proteins, including haptoglobin (Hp), transthyretin (TTR), orosomucoid glycoprotein 1/α1-acid glycoprotein (ORM1), α1-antitrypsin (A1AT), serum amyloid A (SAA), and S100A9. These proteins showed distinct expression patterns between survivors and non-survivors, particularly during the early stages of sepsis. The results highlight significant differences in the proteome of survivors and non-survivors, suggesting that dysregulation of the inflammatory response may be a key factor contributing to mortality in sepsis [43].

N. K. Sharma et al. compared the proteomic profiles of sepsis patients with community-acquired

pneumonia to those of healthy volunteers of the same age and sex. Bioinformatic analysis of differentially expressed proteins in sepsis patients revealed changes in proteins involved in cytoskeleton and cell motility, lipid metabolism, immune response, and other processes [44].

A separate plasma proteomics study of sepsis patients with hospital-acquired pneumonia identified dysregulated lipid metabolism as a key abnormality. The study found lower expression of PON1 and apolipoproteins (ApoA1, ApoC, and ApoE) associated with HDL and higher expression of Hp and SAA1/SAA2. A validation study found lower plasma levels of total cholesterol, HDL-C, LDL-C, non-HDL cholesterol, apolipoproteins (ApoA1 and ApoB100), and PON1 in patients with hospital-acquired pneumonia. These findings are consistent with previous research highlighting the importance of lipid metabolism in the pathogenesis of sepsis [45].

L. Su et al. used proteomic analysis to identify 34 differentially expressed urinary proteins in patients with sepsis and systemic inflammatory response syndrome (SIRS) using iTRAQ (isobaric tags for relative and absolute quantitation) labeling and 2D-LC-MS/MS. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses revealed that these proteins are involved in inflammation, immune response and cytoskeletal organization. A protein-protein interaction network identified five specific proteins: cadherin-1 (involved in actin cytoskeleton remodeling), Hp (with anti-inflammatory properties), complement component 3, SERPINA1 (with pro-inflammatory activity), and ceruloplasmin (which provides antioxidant and anti-inflammatory protection) [46].

The same research group published the results of another study in which proteomic and bioinformatic analyses of urine from sepsis patients with different outcomes (survivors vs. non-survivors) revealed significant differences in protein expression. Five proteins (SELENBP-1, HSPG-2, A-1-BG, HPR, and LCN) were upregulated, while two (LAMP-1 and DPP-4) were downregulated in non-survivors. Three previously unknown differentially expressed proteins (LAMP-1, SBP-1, and HSPG-2) were validated by immunoblotting. LAMP-1 expression was significantly lower in non-survivors, whereas SBP-1 and HSPG-2 levels were similar between survivors and non-survivors. These findings suggest that urinary LAMP-1 levels may be used as a prognostic marker for sepsis outcome [47].

Inflammation-induced blood coagulation amplifies the inflammatory response, resulting in a positive feedback loop [59]. Neutrophils, monocytes, macrophages, platelets, and other inflammatory cells play important roles in the pathogenesis of sepsis. Platelets, as anucleated cellular fragments, are particularly well suited for proteomic analysis to detect protein changes in sepsis. Liu and colleagues used 2-DE (two-dimensional electrophoresis) and MALDI-TOF-MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) to identify proteins differentially expressed in platelets from sepsis patients versus healthy controls. The study found increased expression of five platelet proteins in sepsis patients: EFCAB7 (calcium ion binding), actin (cytoskeletal protein), IL-1β (cytokine), GPIX (membrane receptor), and GPIIb (integrin). These proteins are involved in inflammatory response and coagulation activation, highlighting the critical role of platelets in sepsis-induced inflammation and coagulation [48].

H. Zhang et al. used iTRAQ-based quantitative proteomic analysis to compare changes in the monocyte membrane proteome before and after LPS exposure. A total of 1,651 proteins were identified, of which 53.6% were membrane proteins. Subcellular analysis revealed that more than 90% of mitochondrial membrane-associated proteins were significantly downregulated. This finding suggests that mitochondria may be a primary target of bacterial infection in sepsis [49].

P. M. De Azambuja Rodrigues et al. used LC-MS/MS to detect monocyte proteins in patients with septic shock. Downregulated proteins in sepsis include those involved in oxidative phosphorylation and the Krebs cycle (ATP5C1, DLST, ETFB, NDUFA11, NDUFA2, NDUFS7, NDUFS8, PDK3, PDP1, PDPR, RXRA, SUCLG2, TACO1, and UQCRQ), β-oxidation of fatty acids (ACADM, DECR1, PCCA, and PCCB), and the interferon signaling pathway (EIF2AK2, EIF4A3, EIF4E2, HLA-DPA1, HLA-DQA2, HLA-DRA, HLA-DRB1, IFIT1, MX1, NUP35, OAS3, PSMB8, and UBE2L6), as well as the MHC II antigen presentation pathway (CD74, CTSH, DCTN3, DYNC1LI2, HLA-DMA, HLA-DMB, HLA-DPA1, HLA-DQA2, HLA-DRA, HLA-DRB1, KIF2A, and OSBPL1A). Glycolysis-associated proteins (enzymes PGK1, ALDOA, ALDOC, GADPH, PKLR, GPI, and LDHA) were found to be upregulated. These proteomic findings suggest significant disturbances in monocyte energy metabolism in septic shock patients [50].

In a study of brain autopsies of patients who died from sepsis, the absence of occludin expression in the brain microvascular endothelium was associated with more severe disease progression. Occludin is an essential integral protein for tight junctions in endothelial cells. Erikson and colleagues found that endotoxin and pro-inflammatory cytokines significantly reduced occludin expression *in vitro* in a human brain vascular endothelium model [60]. Thus, blood occludin levels may be a promising biomarker for predicting blood-brain barrier (BBB) damage in sepsis [18].

The role of various cluster of differentiation (CD) receptors as prognostic bio-

markers is also being investigated. For example, in a study by W.-P. Yin et al., nCD64 combined with SOFA score predicted 28-day mortality more accurately than procalcitonin measurement and SOFA score [61]. Resistin and myeloperoxidase (MPO) levels are strongly associated with the development of multiorgan failure. A. Bonaventura et al. found that elevated plasma concentrations of resistin and MPO from the first day of sepsis were associated with the development of organ dysfunction de novo. However, only MPO elevation from day 1 predicted 90-day mortality in sepsis [62].

C. Cao et al. [63], and B. J. Anderson et al. [65] performed studies on the prognostic significance of specific soluble receptors. According to a meta-analysis of 2,418 patients by C. Cao et al., serum sTREM-1 (soluble triggering receptor expressed on myeloid cells-1) had moderate specificity for identifying septic patients. However, when combined with other clinical parameters, it was more predictive of sepsis-related mortality than clinical parameters alone [64]. In a multicenter prospective cohort study by Anderson et al., an sTNFR1 (soluble tumor necrosis factor receptor-1) concentration > 8,861 pg/mL predicted 30-day mortality.

For the first time, the molecular dynamic profiles of serum exosomes and their potential role in the development of sepsis were investigated in 2022 [66]. A multi-omics analysis revealed that the onset of the «cytokine storm» is closely associated with circulating exosomes in the serum of sepsis patients. Specifically, mRNAs (messenger RNAs) in serum exosomes of sepsis patients were associated with cytokine synthesis and secretion. Pre-administration of serum exosomes to septic mice reduced TNF-α and IL-6 mRNA expression in multiple organs, resulting in organ protection. This finding supported the authors' previous study, which found that exosomes isolated from the serum of LPS-induced mice significantly reduced inflammation and improved survival in CLP mice (a septic model involving cecal ligation and puncture) [67].

Furthermore, exosomes from sepsis patients were found to be associated with complement and coagulation cascades, containing proteins from both the classical and alternative complement pathways [66]. This study also demonstrated the role of serum exosomes in modulating the immune response in sepsis by regulating specific vitamin metabolism pathways.

Several studies on increased intestinal permeability in sepsis found elevated levels of zonulin, I-FABP (intestinal fatty acid binding protein) and the D-isomer of lactic acid.

Taken together, metabolomic and proteomic approaches to sepsis provide a plausible framework for describing the biological pathways leading to adverse outcomes.

Clinical phenotyping of sepsis. Clinical phenotyping is required to identify specific groups of patients who may benefit from targeted interventions. Several approaches to phenotyping sepsis patients in the ICU have been proposed, including phenotyping based on temperature trends [70–85], hemodynamic characteristics [86–90], response to fluid therapy (in septic shock) [91–95], ICU outcome (favorable or fatal) [96–101], and characteristics of multiple organ dysfunction [91, 102–109], often using artificial intelligence and machine learning.

The key findings of these studies are discussed below.

In recent years, attempts have been made to classify sepsis based on body temperature parameters. According to research in this area, hypothermia (or absence of fever) in sepsis patients is independently associated with higher mortality [70, 72, 73]. A 2017 meta-analysis found that fever in septic patients is a protective factor that reduces mortality compared to normothermia [71]. A Russian retrospective study found that hypothermia in sepsis patients was associated with more severe arterial hypotension, acidosis, and increased INR [85].

This supports the idea that therapeutic hyperthermia in patients with hypothermia may improve sepsis survival. Several clinical trials have found an association between improved outcomes and warming of hypothermic sepsis patients [83, 84]. However, the study by A. M. Drewry et al. [83] has a significant limitation that prevents its findings from being directly translated into routine clinical practice. Specifically, almost twice as many patients in the hyperthermia group tested positive for pathogens susceptible to empirically prescribed antibiotics. Honore et al. pointed out this limitation in a letter to the editor of *Critical Care Medicine* [110].

Before discussing the results of the following sepsis phenotyping studies, it is necessary to briefly explain machine learning and cluster analysis, which serve as the methodological basis for many of these investigations.

In recent years, artificial intelligence (AI) has been increasingly applied in medicine. The basic idea behind AI, particularly machine learning in biomedicine, is to train an information system on large data sets (clinical, laboratory, imaging, etc.) to recognize and extract specific patterns. This allows for the grouping and subsequent analysis of these patterns.The next step in this process is cluster analysis.

Cluster analysis quantifies the similarities among patients in a heterogeneous population. This method generates groups of patients (essentially representing different phenotypes) without relying on predetermined hypotheses [111]. However, a limitation of cluster analysis is the difficulty in determining the optimal number of data clusters.

Group-based modeling is an extension of cluster analysis that identifies groups of patients who exhibit similar trends with respect to a particular variable of interest [112].

A study by S. V. Bhavani et al. used group-based modeling to identify sepsis subphenotypes based on temperature trend patterns. Four distinct subphenotypes were identified: normothermic, hyperinflammatory («hyperthermic, slow resolvers»), hypoinflammatory («hypothermic»), and a balanced inflammatory subphenotype («hyperthermic, fast resolvers») — the latter being associated with the lowest mortality rate [74]. The same research group validated their findings in a separate retrospective study that identified four similar phenotypes in COVID-19 patients [78].

Hemodynamic characteristics in sepsis and septic shock, as shown in recent studies, may also help to address the clinical heterogeneity of sepsis patient populations.

The introduction of continuous hemodynamic monitoring in routine ICU practice has made it possible to define different phenotypes based on hemodynamic profiles.

In a study by R. M. Nowak et al., cluster analysis of invasive hemodynamic monitoring data from 127 patients identified three phenotypes with distinct hemodynamic profiles:

- Phenotype I (56.7%): High cardiac index (CI) and normal systemic vascular resistance index (SVRI).
- Phenotype II (39.4%): Low CI and elevated SVRI.
- Phenotype III (3.9%): Very low CI and very high SVRI.

The three phenotypes differed significantly in terms of 30-day mortality: 5.6% for patients with phenotype I and 20% for patients with phenotypes II and III [86].

J.-L. Zhu et al. analyzed trends in systolic blood pressure (SBP) in more than 3,000 sepsis patients admitted to the ICU and identified seven distinct phenotypes [90]. The lowest mortality was observed in patients with phenotype 3. The authors suggest that the SBP trend characteristic of phenotype 3 should be considered as a hemodynamic target for sepsis patients during the first 10 hours after admission to improve outcomes. In addition, when comparing phenotypes 2 and 6, they found that persistent hypotension was associated with a worse prognosis than a rapid decline in SBP. Applying the findings of this study, clinicians could use SBP trend monitoring to earlier identify high-risk patients [90].

A multicenter study investigating the relationship between septic cardiomyopathy phenotypes — defined by echocardiographic characteristics — and sepsis outcomes is ongoing [89]. Preliminary results from this study have identified phenotypes with different responses to fluid therapy.

In addition, a multicenter randomized controlled trial (RCT) is underway to determine whether a strategy based on clinical hemodynamic phenotyping, with a focus on capillary refill time (CRT), can improve clinical outcomes compared to standard of care [95].

Thus, approaches to hemodynamic management of sepsis and septic shock can be tailored by identifying distinct phenotypes among the diverse population of sepsis patients. Infusion and catecholamine support protocols can be modified based on phenotype, allowing for individualized and adaptive care for each ICU patient.

In 2019, C. W. Seymour et al. published the SENECA study [104]. The study used machine learning to analyze data from more than 63,000 patients and identified four novel sepsis phenotypes (α, β, γ, and δ). These phenotypes were distinguished by unique demographic profiles, laboratory markers, and patterns of organ dysfunction. Treatment outcomes modeled with data from three randomized clinical trials (including 4,737 patients) demonstrated sensitivity to changes in phenotype distribution. The phenotypes include:

- α phenotype: Approximately one-third of sepsis patients have minimal laboratory abnormalities, limited organ dysfunction, and the lowest in-hospital mortality (23%).
- β phenotype: Found in 27% of patients, associated with advanced age, chronic comorbidities, and higher risk of acute kidney injury.
- γ phenotype: Approximately 25% of patients, similar to the β phenotype but with elevated inflammatory markers and a prevalence of pulmonary dysfunction.
- δ phenotype: The least common (13%) and most severe phenotype, characterized by severe multi-organ failure, including liver dysfunction and refractory shock, with the highest in-hospital mortality (32%).

Retrospective analysis revealed persistent differences between phenotypes. The cumulative 28-day mortality rates were 5% for the α phenotype, 13% for β, 24% for γ, and 40% for δ. In all cohorts and studies, the δ phenotype had significantly higher 28-day and 365-day mortality rates than the other three phenotypes ($P < 0.001$). Early targeted therapy according to the Rivers protocol [113] was found to be detrimental in patients with the δ phenotype, based on retrospective analyses of more than half of the RCTs included in the study. The endophenotypes aHUS and MAS, which comprise a significant proportion of the δ phenotype as defined by C. W. Seymour et al., may share a common pathogenesis. Endotoxin is an important molecular target for the δ phenotype, activating both the complement and cytokine pathways. Patients susceptible to endotoxin may develop MAS, aHUS-like syndrome, or both [114,115].

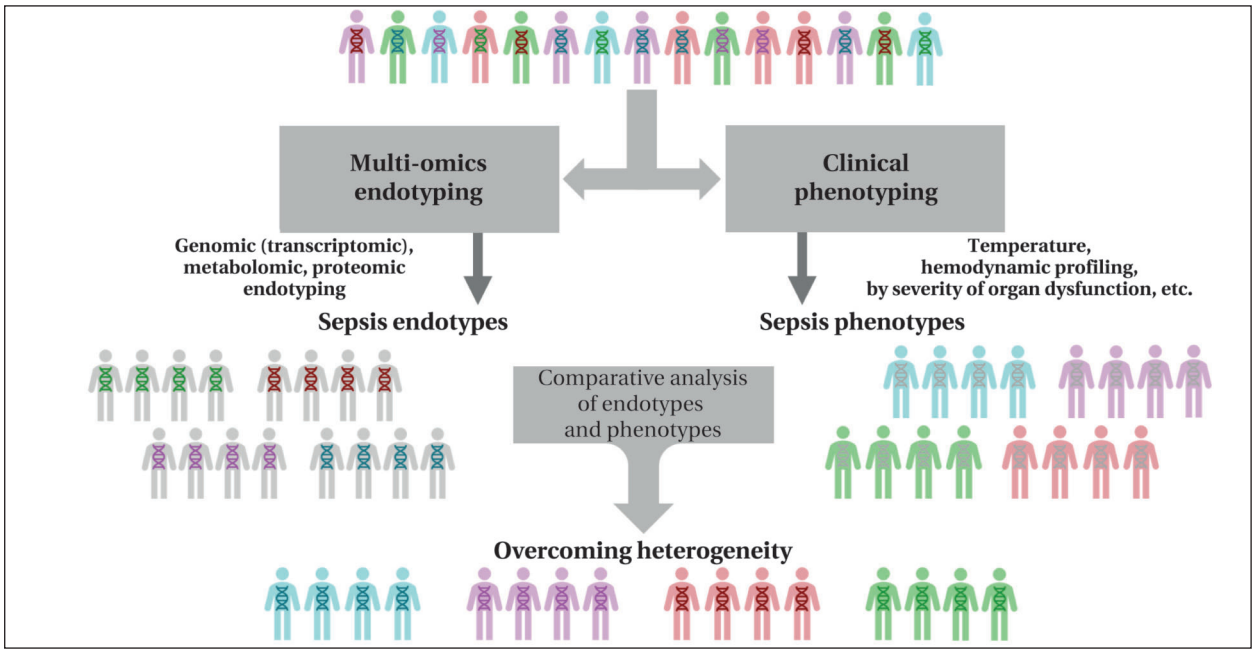

Fig. 2. A possible way to overcome the heterogeneity of sepsis patients.

It is worth noting that the study by C. W. Seymour et al. [104] was neither the first nor the only attempt to identify patterns in the population of patients with sepsis. We identified three studies in which the authors attempted to phenotype the heterogeneous syndrome of multiple organ dysfunction syndrome (MODS) in sepsis [91, 102, 103]. All three studies used machine learning methods, resulting in four phenotypes that significantly differed in the profile of organ dysfunction within MODS. Since 2019, the results of five additional studies on clinical phenotyping of MODS in sepsis have been published [105–109].

Recently, the results of a Russian study on the identification of clinical phenotypes of sepsis in patients with severe community-acquired pneumonia based on the SENECA system proposed by C. W. Seymour et al. were published [104, 116]. Four sepsis phenotypes were identified in all patients: α (48.6%), β (19.3%), γ (13.1%) and δ (19%). The majority of patients with viral pneumonia belonged to the α phenotype (51.9%), whereas the δ phenotype predominated in patients with bacterial pneumonia (55.2%). The highest mortality rates were observed in patients with the β phenotype of sepsis associated with bacterial (7 deaths out of 7 cases) and viral pneumonia (115 deaths out of 121 cases). Interestingly, in patients with the α phenotype of sepsis and severe community-acquired pneumonia caused by COVID-19, therapy with interleukin-6 receptor-targeting monoclonal antibodies resulted in favorable sepsis outcomes in 87.5% of cases [116].

The research of Y. Qin et al. has practical implications. The authors used 24-hour machine learning techniques to identify four computable pediatric sepsis phenotypes. Among these, the authors identified one phenotype (PedSep-D) as particularly suitable for inclusion in early personalized research focused on multiple organ dysfunction associated with thrombocytopenia and macrophage activation syndrome. The study resulted in a mathematical model capable of identifying pediatric sepsis phenotypes using 25 parameters available within the first 24 hours of hospitalization [117].

Although incorporating phenotyping into routine clinical practice may seem difficult due to the complexity of centralized clinical data collection and the sophistication of machine learning and cluster analysis methods, initial steps in this direction are already underway. Clinical phenotyping of the diverse sepsis patient population will enable a more personalized approach to care, significantly improving the precision and selectivity of treatments. There is no doubt that this global trend will continue and the amount of research in this area will only increase.

Analysis of sepsis subtype combinations as a potential strategy to overcome heterogeneity A secondary analysis of the prospective MARS cohort study [13] aimed to compare sepsis subtypes using clinical, biomarker, and transcriptomic data from sepsis patients [118]. While molecular subtypes derived from transcriptomic data can now be reliably identified, finding meaningful correlations between these molecular subtypes and clinical phenotypes remains challenging. The concordance between subtypes defined in studies such as SENECA [104], ARDS [119, 120], MARS [13] and SRS [8] was moderate to low, suggesting that each subtype represents a distinct patient cohort.

These findings suggest that the identified endotypes and phenotypes represent distinct, potentially complementary aspects of sepsis subtypes. The authors propose a combined approach that includes molecular genetic endotyping and clinical phenotyping of the diverse sepsis population. This integrated strategy improves the accuracy of patient assessment. However, as R. B. E. van Amstel et al. note, it also presents significant challenges.

First, effective stratification requires large sample sizes. Second, the lack of alignment between omics and non-omics data types creates inherent difficulties in integrating them. Nevertheless, the long-term goal of all sepsis typing methods should be the same: to stratify patients into as homogeneous subgroups as possible [118].

Ultimately, improving the accuracy of stratification techniques has the potential to help overcome the inherent heterogeneity of sepsis in the future.

Conclusion

Classification of heterogeneous populations based on molecular endotypes and multi-omics profiling of sepsis patients may soon provide effective tools for targeted therapies tailored to specific subgroups of patients. This approach may allow the use of molecular biomarkers in sepsis both for patient selection and for monitoring the efficacy of specific (immunobiologic) therapies.

The identification of distinct biological patterns has the potential to facilitate the rational inclusion of sepsis patients in clinical trials, as well as to improve diagnosis, prognosis and personalized therapeutic strategies. This includes modulation of the immune response to sepsis (Fig. 2).

Future efforts must focus on developing new strategies based on a personalized assessment of the patient's genetic, metabolomic and proteomic response to infection, as well as the clinical sepsis phenotype. Establishing links between these elements and identifying targets for precision sepsis therapies are among the most critical challenges for the medical research community in the coming years.

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