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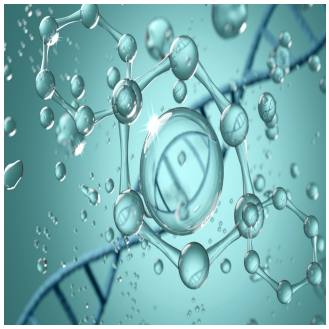
Deciphering Sepsis: Transforming Diagnosis and Treatment



Sepsis is a major but often overlooked cause of death and disability. In 2017, there were an estimated 48.9 million cases of sepsis, causing 11 million deaths worldwide. Sepsis is more common in lower-income regions, and its incidence is expected to rise as populations age. Severe forms of sepsis, such as septic shock, have high mortality rates, and even survivors face long-term health complications like post-sepsis syndrome.

Despite its significant impact, sepsis is often under-recognised in global health reports due to its diverse causes, symptoms, and association with other health conditions. There is also a lack of consensus on a clear definition, complicating diagnosis and treatment.

Systems immunology could transform sepsis management by identifying early immune dysfunction, categorising sepsis into distinct mechanistic subgroups (endotypes), and developing precision therapies. These advancements could improve diagnosis, treatment, and outcomes for sepsis and related conditions like long COVID.

Systems immunology uses advanced computational and statistical techniques, including AI, machine learning, network biology, and biomarker discovery, to analyse genome-wide data and generate new hypotheses about complex systems like sepsis. It involves aggregating various types of omics data, such as genetic variations (from GWAS), changes in gene and microRNA expression (transcriptome and microRNAome), protein or lipid alterations (proteome and lipidome), metabolite variations (metabolome), and epigenetic modifications that affect how DNA is read. This comprehensive approach helps deepen understanding of immune system behaviour in conditions like sepsis.

Each element of systems immunology can be analysed on a genomic scale, though the accuracy of coverage varies. The transcriptome, which is obtained through RNA-Seq (high-throughput sequencing of cDNA from expressed messenger RNAs), provides the most comprehensive and accurate real-time data.

Systems biology and immunology analyse data to identify differences associated with diseases or treatments, revealing emergent properties that offer new insights. Instead of focusing on individual elements, systems analysis looks at how components integrate to understand new biological concepts. Clustering is a key technique used to group elements based on common features, like gene functions or pathways.

Combining different omics approaches (multiomics) — such as genomics, proteomics, and metabolomics — could provide a more comprehensive understanding of complex diseases like sepsis. By integrating these datasets, researchers can uncover new biomarkers and therapeutic targets, improving patient care and health outcomes. Multiomics methods should be increasingly utilised in sepsis research to enhance our understanding and develop better treatment strategies.

Sepsis has a high mortality rate due to two main factors: challenging and often delayed diagnosis and the lack of sepsis-specific treatments. The difficulty in diagnosing sepsis, especially in its early stages, can lead to delays in administering treatments like antibiotics or antivirals. These delays significantly increase mortality rates, with studies showing that for every hour of delay in appropriate antibiotic treatment, in-hospital mortality can rise by up to 7.6% in cases of septic shock.

Early diagnosis of sepsis is challenging due to its non-specific symptoms, such as changes in temperature, blood pressure, respiratory rate, and heart rate. According to the Sepsis-3 criteria, sepsis is diagnosed when there's a documented or suspected infection along with organ dysfunction, indicated by a two-point increase in the Sequential Organ Failure Assessment (SOFA) score. However, the early-SOFA score

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(qSOFA) has low accuracy, missing over half of sepsis cases. The gold standard for detecting infection is bacterial identification through blood or tissue cultures, but many sepsis cases are culture-negative. Rapid identification methods also fail to detect the pathogen in most cases, possibly because sepsis progression may not require the live pathogen or involves non-culturable bacteria, fungi, or viruses. Additionally, even positive cultures may not indicate "true" sepsis, as colonisation can be mistaken for infection, especially in patients with comorbidities.

To improve sepsis diagnosis, researchers have explored changes in the host's response, especially inflammatory biomarkers, as proxies for infection. While C-reactive protein and procalcitonin show the most potential, others like IL-6, TREM-1, presepsin, and calprotectin are also used, though these tests struggle with early sepsis detection and lack specificity. Gene expression signatures, based on whole-blood transcriptomics, are emerging as a promising tool for diagnosing and predicting sepsis. Despite varying accuracy, some gene expression signatures can classify 68-84% of sepsis cases but often fail to distinguish between sepsis and conditions like cancer, cardiac disease, or inflammatory bowel disease.

Machine learning-based gene expression signatures in sepsis often show moderate accuracy, with many focusing on non-specific inflammatory responses. However, two signatures, the cellular reprogramming (CR) signature and its condensed version, SepsetER, stand out.

Studies involving a large number of adults have shown that transcriptional changes can occur before the onset of sepsis symptoms, suggesting that early prediction of sepsis might be possible. Similar observations have also been made in neonates.

The European Group on Immunology of Sepsis has identified the need to understand the dynamics of sepsis-associated immune alterations, as immune dysfunction varies greatly over time. Analysing a single time point, such as hospital or ICU admission, can help identify predictive biomarkers and potential treatments but doesn't capture the full complexity of the disease's progression. Longitudinal studies, which track gene expression over time, are more informative in understanding individual disease trajectories and overcoming patient-to-patient heterogeneity.

Studies of sepsis progression have identified trends like immune suppression, disrupted cell cycle control, and increased inflammation. Recent longitudinal research of ICU patients with sepsis (including those with and without COVID-19) found common immune dysfunction, such as upregulation of IL-1 signalling and inflammatory cytokines. COVID-19 patients showed a robust antiviral response at ICU admission, but after a week, their immune profiles became similar to non-COVID-19 sepsis patients, suggesting that severe COVID-19 is a form of sepsis, with immune dysregulation being the primary concern rather than the pathogen itself.

Gene expression studies have explored post-sepsis and post-COVID conditions, identifying persistent immune dysregulation in patients with long-term symptoms. A cohort of COVID-19 survivors showed different immune responses, with four distinct endotypes based on T-cell and monocyte gene expression. These endotypes revealed patterns linked to the severity of acute illness and long-term sequelae. A separate RNA-Seq study identified three endotypes in post-COVID patients, showing distinct immune responses in patients who did or did not develop long COVID symptoms. The "Resolved" endotype showed resolution of inflammation after discharge, while the "Suppressive" and "Unresolved" endotypes exhibited ongoing immune issues, highlighting the need for personalised approaches to treatment and recovery.

Further research into epigenetic mechanisms could lead to new biomarkers and therapeutic approaches for sepsis and its long-term effects. Animal studies have shown that epigenetic therapies, such as DNA methyltransferase and histone deacetylase inhibitors, may reverse some sepsis-related changes, offering the potential for treating sepsis and its long-term consequences.

During the early stages of the COVID-19 pandemic, it was recognised that many severe cases of COVID-19, particularly those requiring respiratory support or resulting in death, were a form of viral sepsis. This aligns with findings from clinical records and systems immunology, showing similar immune mechanisms between COVID-19 sepsis and bacterial sepsis. These pandemics highlight the importance of sepsis in global health crises and emphasise the need for novel, pathogen-agnostic diagnostic tools and treatments that could address severe disease outcomes in future pandemics, even before a pathogen is identified.

A coordinated, multi-stakeholder approach is crucial, including the establishment of programmes like the 2030 Global Agenda for Sepsis, which aims to reduce global sepsis incidence, improve survival rates, and decrease healthcare costs.

Challenges in clinical prediction models, such as those seen in schizophrenia, suggest the need for tailored approaches in sepsis research. To overcome these challenges, researchers should focus on capturing heterogeneity through phenotyping, identifying relevant study characteristics, and utilising longitudinal validation methods. Importantly, incorporating multiomics approaches in sepsis models has demonstrated their generalisability and potential to significantly improve sepsis care on a global scale.

Source: Frontiers in Science
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