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The challenge of sepsis

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A Viewpoint on the Frontiers in Science Lead Article

Deciphering sepsis: transforming diagnosis and treatment through systems immunology

Key points

- The heterogeneity of sepsis makes diagnosis, and therefore precision therapy, very challenging.
- Systems immunology coupled with machine learning techniques can identify endotypes that may allow more precise diagnosis and therefore more targeted treatment.
- Examining analogies between long COVID, post-sepsis, and chronic fatigue syndromes may shed light on the underlying pathology and offer opportunities for improved treatment.

Introduction: the challenge of sepsis

To paraphrase Jane Austen, it is a truth universally acknowledged that sepsis has been one of the most difficult and frustrating clinical challenges of the last 50 years. Despite literally thousands of scientific papers and tens of thousands of patients enrolled in clinical trials, the clinical syndrome that we call sepsis continues to be responsible for approximately 20% of all deaths worldwide (1). Unlike some of the major infective challenges that are largely restricted to certain geographical regions—such as malaria in sub-Saharan Africa and East Asia or gastrointestinal infections in South Asia—sepsis is a global threat, as recognized by the World Health Organization (WHO) in its 2017 Resolution (2). It is a sobering thought that even the most advanced economies deploying sophisticated intensive care methods have made only modest inroads into reducing sepsis-related mortality. Why has this been so difficult?

Diagnosing sepsis

As Hancock et al. point out in their lead article (3), sepsis is a prototypic syndrome with a bewildering array of symptoms and signs, a multitude of causes, and an impact that stretches from a relatively mild self-limiting illness to an acute, life-threatening

disease. Little wonder, then, that it has proved so challenging. The difficulties in establishing a single epidemiological definition have made it almost impossible to enroll a homogeneous population into clinical trials, greatly hindering the investigation of new treatments. Meanwhile, at the bedside, it is usually relatively junior clinical staff who often struggle to recognize the condition in time to start early treatment. Hancock et al. make the case that the use of systems immunology tools has the potential to dissect this heterogeneous population into specific subgroups —"endotypes"—early in the clinical presentation to help predict the disease course and select treatments that will specifically address the pathological molecular dysfunction. This approach —an example of the concept of precision medicine—will depend for its success on (at least) three elements. First, it requires that the "omics profile" is consistent and reproducible in terms of the clinical phenotype and the clinical and geographic context of the patient. This is still a work in progress; Garduno and others (4) have helpfully reviewed the range of different approaches to creating stable endotypes. Second, it will be important to understand how these endotypes evolve longitudinally in individual patients, a point rightly emphasized by Hancock et al. One of the clinical challenges is that patients with sepsis present at widely differing points during their clinical course; we need to understand how the omics profile changes over time and how this should be interpreted. Finally, on a practical level, all of this depends on the availability of simple, widely available diagnostic tests that can be used quickly and easily in emergency departments. This is still a long way off.

Are omics-based endotypes alone sufficient to identify patients adequately and allow specific therapeutic interventions? Garduno et al. (4) summarize a number of small clinical trials in which immunologic manipulations were deployed based on an immunophenotypical abnormality. Thus far, the outcomes have not been particularly successful. One component of the equation that seems to be missing at present is the causative organism, a point also made by others (5). While sepsis is in many respects a final common pathway of injury following infection, different bacteria (and viruses) lead to quite different clinical and immunologic effects. For instance, *Streptococcus pyogenes*, a Gram-positive bacterium, can be associated with a toxic shock-like syndrome attributed to a superantigen effect, while the Gram-negative *Vibrio vulnificus* is associated with sepsis and necrotizing skin lesions. The challenge will be to incorporate complex omics data together with clinical and microbiologic information into what one might call an individual "therapeutic prescription".

Post-sepsis, long COVID, and chronic fatigue syndrome—one and the same?

One of the most intriguing insights to emerge in the post-COVID era is the apparent similarity between three seemingly distinct conditions. Chronic fatigue syndrome (CFS, known also as myalgic encephalitis or post-viral syndrome) has long been recognized as a variable constellation of symptoms and signs that often, but not always, follows an acute viral infection such as Epstein-Barr virus. Characterized by profound fatigue lasting many months, and sometimes years, and a myriad of inconsistent immunologic findings, it has long frustrated both clinicians and patients because of the lack of a single diagnostic test and the absence of any effective treatment. Post-sepsis syndrome (PSS), recognized more recently, refers to the physical—and in particular the neurocognitive—and neuropsychological consequences following acute sepsis. Finally, long COVID (or post-COVID syndrome), one of the most consequential long-term effects of the pandemic, also shows a wide range of manifestations, including significant neuropsychiatric, cardiovascular, and autoimmune phenomena, associated with evidence of immune dysregulation, mitochondrial abnormalities, and alterations of the microbiome (6). Hancock and colleagues (3) focus on the similarities between PSS and long COVID and describe gene expression studies that distinguish patients with an uncomplicated course from those who go on to develop long COVID. They speculate that epigenetic mechanisms may influence the development of both syndromes. Once again it seems to be possible to identify endotypes —that is, transcriptional patterns that co-locate with clinical phenotypes to identify different responses to acute infection.

The challenge here is to disentangle the various clinical pathways that may be involved. Thus, patients with severe COVID often have a sepsis-like syndrome and are transferred to intensive care units (ICUs). If they develop persistent long-term symptoms, are they suffering from long COVID, or PSS, or simply post-ICU syndrome? But maybe, as Hancock et al. suggest, that is exactly the point: it does not really matter what label one attaches if indeed there is a shared pathological process. Elucidating the mechanism of these disease processes could perhaps allow therapeutic strategies applicable to all three disorders.

A global perspective

As Hancock et al. point out, the extraordinary capability of systems biology supported by machine learning and artificial intelligence models offers the possibility of "getting under the skin" of the heterogeneity of sepsis and being able to identify subgroups of patients whose disease will evolve in a particular way, and perhaps even specifying "therapeutic prescriptions" for individual patients. It remains to be seen if this promise can be translated into actionable clinical decision-making tools. If it can, it is unrealistic to expect that it will be available to people in low- and middle-income countries, where the incidence of sepsis-related death is perhaps 50-fold higher than in high-income countries (7). Hancock et al. argue that sepsis (or at least, a clinical syndrome akin to sepsis) underlies most of the morbidity and mortality that accompanies serious pandemic infections, and a more precise diagnosis will support more

effective treatment. The WHO rightly points out that prevention (e.g., good personal hygiene, avoiding unclean water or poor sanitation, ensuring high vaccine uptake, and breastfeeding for newborns) is the best approach to mitigating serious infection (8). Both strategies are worthy of further attention.

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References

1. Meyer NJ, Prescott HC. Sepsis and septic shock. *N Engl J Med* (2024) 391 (22):2133–46. doi: 10.1056/NEJMra2403213

2. World Health Organization. Improving the prevention, diagnosis and clinical management of sepsis [resolution WHA70.7]. Seventieth World Health Assembly (2017). Available at: https://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R7-en.pdf

3. Hancock REW, An A, Dos Santos CC, Lee AHY. Deciphering sepsis: transforming diagnosis and treatment through systems immunology. *Front Sci* (2025) 2:1469417. doi: 10.3389/fsci.2024.1469417

4. Garduno A, Cusack R, Leone M, Einav S, Martin-Loeches I. Multi-omics endotypes in ICU sepsis-induced immunosuppression. *Microorganisms* (2023) 11 (5):1119. doi: 10.3390/microorganisms11051119

5. Giamarellos-Bourboulis EJ, Aschenbrenner AC, Bauer M, Bock C, Calandra T, Gat-Viks I, et al. The pathophysiology of sepsis and precision-medicine-based immunotherapy. *Nat Immunol* (2024) 25(1):19–28. doi: 10.1038/s41590-023-01660-5

6. Fleischmann-Struzek C, Joost FEA, Pletz MW, Weiß B, Paul N, Ely EW, et al. How are long-Covid, post-sepsis-syndrome and post-intensive-care-syndrome related? A conceptional approach based on the current research literature. *Crit Care* (2024) 28 (1):283. doi: 10.1186/s13054-024-05076-x

7. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *Lancet* (2020) 395(10219):200–11. doi: 10.1016/S0140-6736(19)32989-7

8. World Health Organization. Sepsis [online] (2024). Available at: https://www.who.int/news-room/fact-sheets/detail/sepsis