Charting a course for precision therapy trials in sepsis

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Sepsis is a leading cause of death worldwide, accounting for approximately 11 million deaths annually in non-pandemic years.[1] During the COVID-19 pandemic, a single pathogen was responsible for at least 5·9 million deaths and possibly far more,[2] accentuating the historic role of infection as a force of population selection that has shaped global genetic architecture. The current consensus definitions of adult and paediatric sepsis identify sepsis as a dysregulated host response to infection that results in life-threatening organ failure,[3,4] recognising that two patients infected with the same pathogen at the same body site could have strikingly different clinical presentations; for example, one might present with septic shock and multiorgan dysfunction, whereas the other might manifest only fever and localised symptoms. However, a biological explanation of this heterogeneity remains elusive. For almost four decades, the critical care community has sought to determine the features of the dysregulated host response that matter during sepsis. Concurrent excessive inflammation and hypofunctional cellular immunity characterise patients with sepsis, but separating the epiphenomena from causal contributors has been challenging. To date, sepsis therapy directed at the host response remains in its infancy. If precision therapy for sepsis is to be realised, it will require a clearer understanding of the molecular events that determine organ injury, knowledge of which events are reversible and in what timeframe, and the ability to identify the specific biological derangements rapidly during clinical care.

Two papers in *The Lancet Respiratory Medicine*[5,6] enhance this effort by emphasising key principles in sepsis immunobiology that warrant further investigation and by highlighting advances in the categorisation of aberrant immune events. In a Personal View, Manu Shankar-Hari and colleagues[5] argue for a revised paradigm of sepsis immunobiology by returning to first principles of immunology and microbiology. The authors remind us that humans have multiple lines of protection from microbial threat: avoidance or prevention of infection; resistance to the pathogen's effects; and disease tolerance, whereby avoidance of tissue injury takes primacy over pathogen elimination. Pathogen resistance pathways have been studied extensively in human sepsis, in which substantial heterogeneity in hyperinflammatory protein expression and immunosuppressive cellular and gene-expression programmes is associated with differential survival, complications, and, potentially, treatment effects in randomised trials.[7–9] The proposed reframing of sepsis immunobiology aims to account for pathogen features such as the scale of the microbial threat—which varies with virulence, organismal load, and the proportion of live versus dead microbes—and would enable consideration of dysregulation in the resistance response relative to this threat when planning new therapeutic trials.

Beyond resistance, the Personal View posits that failures in disease tolerance might also contribute to sepsis pathophysiology. Disease tolerance often explains the differential susceptibility of varied species to some infections. For instance, the immune system of many bat species has evolved enhanced interferon-α expression and dampened activation of NLRP3 inflammasome signalling, which probably explains why bats harbour deadly (to humans) viruses such as Ebola, Marburg, SARS-CoV, SARS-CoV-2, and MERS-CoV without manifesting illness, thus allowing zoonotic transmission.[10] Less is known about which pathogens are tolerated by humans and we have no indicators to distinguish a tolerant host from an infected host with impending organ failure; identification of such a marker might offer a simple approach for clinically distinguishing colonisation from pathological infection. Shankar-Hari and colleagues also encourage more focus on immune resilience, or the ability to restore immune homoeostasis, and on dysfunctional resolution programmes, which have been historically under-investigated as potential therapeutic targets in sepsis.

Comprehensive consideration of the many potentially dysregulated immune events during sepsis would be clinically useful, but we currently have few tools to quantify these dysfunctional states in real time. A Review by Sara Cajander and colleagues[6] offers some navigation towards precision sepsis immunotyping by summarising progress and opportunities to better understand patients' immune states. The Review advocates for more specific immune profiling, including the use of multimarker panels of inflammatory proteins and combined profiling of proteomic, metabolomic, and

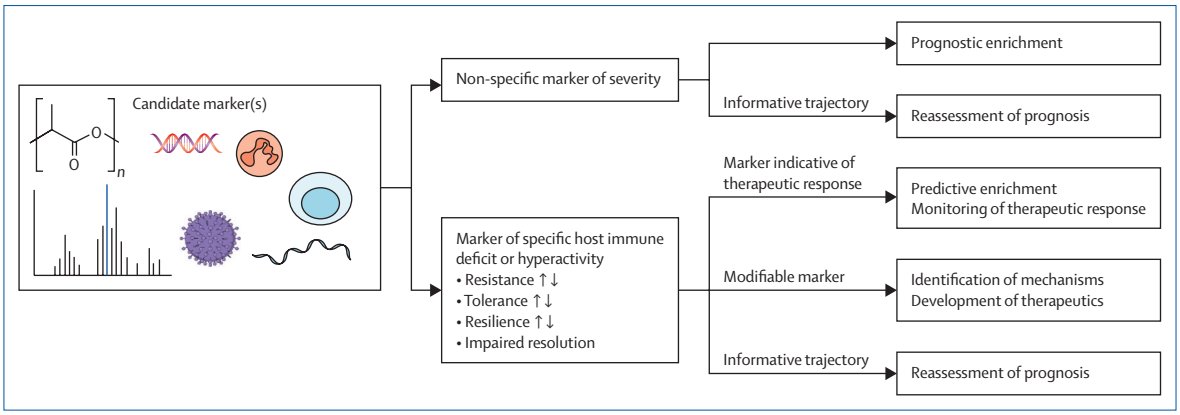

Figure: **Leveraging host immune profiling in sepsis precision medicine**
Among the many potential candidate markers, distinguishing the features that contribute causally to sepsis and that indicate specific pathology will advance precision therapeutics. Whereas non-specific markers of severity can be indicative of prognosis and could inform the selection of trial participants who are more likely to have severe outcomes (prognostic enrichment), they are less informative for predicting therapeutic response. By contrast, markers that can be linked to a specific immune dysregulation are prime candidates to test for the selection of trial participants who are likely to have a therapeutic response on the basis of a biological mechanism (predictive enrichment). Increased specificity should enable greater insights into dysregulated sepsis biology, which might provide opportunities for novel treatment strategies.

cytometric features. Cajander and colleagues stress the utility of functional tests of the immune system, such as tests for viral reactivation or the ex-vivo responsiveness of immune cells to stimuli. Technical barriers—ie, that biomarkers have not received accreditation as clinical tests and that current assays are expensive, time-consuming, or computationally intensive—seem likely to be overcome in the near future, yet major challenges to the implementation of precision immune assessments remain. Among the most urgent issues are the need to understand which features of immune dysregulation contribute causally to sepsis outcomes, which markers most easily and reliably identify specific dysregulation, and which traits are modifiable (figure). By embedding this sophisticated immune profiling within randomised clinical trials, we could determine whether immune parameters might also function as indicators of therapeutic response, and whether immunological trajectories convey information not captured on day zero. Moreover, if new markers of immune resilience and resolution can be validated, perhaps some patients could be treated less aggressively, allowing their endogenous systems to restore function without risking the side-effects of further intervention.

Immune-mediated disease arises from the perturbation of a highly tuned network of danger signals, effector cells, and counter-regulatory stimuli. Manipulation of this system during an episode of sepsis requires careful navigation to ensure that clinicians' best intentions do not further disrupt a balance that is difficult to restore. Validation of the key immunological markers of the dysregulated host response could help to chart a course towards precision-guided trials and therapy for sepsis.

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