Editorial

It ain't what you do (it's the way that you do it): modulating the host response in sepsis

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There is no proven pharmacological intervention for sepsis. This is not for want of trying – dozens of therapies have been studied in clinical trials. Nor is it because of ignorance. Although imperfect, our understanding of the host response to infection has improved dramatically over time. Importantly, it is not due to a scarcity of patients. In England, 45,000 patients are admitted to intensive care units for sepsis annually [1] and, globally, sepsis claims the lives of nearly 3 million children under the age of five each year [2].

Robey et al. offer a meticulous meta-analysis of immunomodulatory therapies in sepsis, examining 56 randomised controlled trials across 20 drug classes [3]. The majority (51 trials) did not show a mortality benefit. Nevertheless, by grouping interventions based on broad mechanism, the authors noted potential benefits associated with anti-inflammatory treatments and cytokine inhibitors. While this may be an important signal, the small size of many trials and the high risk of bias evident in some, mean that these data must be interpreted cautiously. This raises an important question: despite having had the means, motive and opportunity, why have successful interventions for sepsis not been developed?

Modulating what?

While sepsis has been recognised for millennia, the notion of a `sepsis syndrome´ arose in the late 1980s, leading to a consensus definition and the establishment of the systemic inflammatory response syndrome (SIRS) criteria, known as SEPSIS-1 [4] (Table 1). This framework identified sepsis as a set of simple physiologic disturbances occurring in the presence of confirmed or suspected infection. While highly sensitive, these criteria conflated conserved physiological responses with dysregulated immunity. The net result was a dramatic increase in the incidence of sepsis without a proportional rise in the numbers of patients presenting with infection and organ dysfunction. Subsequent revisions have aimed to better identify the latter group, including the inclusion of `severe sepsis´ in SEPSIS-1 and expanded diagnostic criteria in SEPSIS-2 [5] (Table 1).

In 2015, recognising the limited construct validity of previous definitions, sepsis was redefined as ``*life-threatening organ dysfunction caused by a dysregulated host response to infection*´´ and the SIRS criteria replaced with an acute increase of ≥ 2 sequential organ failure assessment (SOFA) points (SEPSIS-3) [6] (Table 1). This identified a smaller population, with worse organ dysfunction and a greater risk of death [1]. These clinical definitions are prognostic: they are useful in clinical practice by providing an objective means of classifying patients at high risk of poor outcomes, facilitating early recognition, supportive management, quality improvement and epidemiological characterisation. However, while they

Table 1 Sepsis definitions.

	Definition	Details
Sepsis-1 [4]		
Sepsis	The systemic response to infection (proven or suspected), manifested by ≥ 2 SIRS criteria	SIRS criteria ▪ temperature < 36°C or > 38°C ▪ heart rate > 90 beats min^{-1} ▪ respiratory rate > 20 breaths min^{-1} or $PaCO_2$ < 4.27 kPa ▪ white blood cell count < 4 or > 12 x 10^9 l^{-1} or > 10% immature forms
Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension	Hypoperfusion abnormalities include lactic acidosis, oliguria and acute alterations of mental status. Hypotension is defined as a systolic blood pressure < 90 mmHg or a reduction of ≥ 40 mmHg from baseline
Septic shock	Severe sepsis with hypotension persisting despite fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction	Patients who are receiving inotropic or vasopressor drugs may not be hypotensive at the time that perfusion abnormalities are measured
Sepsis-2 [5]	Sepsis-1 definitions retained but clinical criteria expanded and a system introduced for the staging of sepsis progression (PIRO)	
Sepsis-3 [6]		
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection. Severe sepsis removed	Organ dysfunction defined as an acute change of ≥ 2 SOFA points*
Septic shock	Sepsis with persistent hypotension requiring vasopressors	Defined as the requirement for vasopressors to maintain mean arterial pressure ≥ 65 mmHg and serum lactate > 2 mmol l^{-1} despite adequate volume resuscitation

SIRS, systemic inflammatory response syndrome; PIRO, Predisposition, Insult infection, Response and Organ dysfunction.
*The Sequential Organ Failure Assessment (SOFA) score has six components: respiratory system (PaO_2/F_iO_2 ratio); nervous system (GCS); cardiovascular system (mean arterial pressure or administration of vasopressors); liver (bilirubin); coagulation system (platelet count); and renal system (creatinine or urine output).

provide information on the likely outcome, they ignore underlying causal mechanisms and give no information regarding which patients are likely to respond to different treatments. Simply refining definitions will not address this; the dysregulated immune response to infection is too heterogeneous, too complex and has too much temporal variation. Instead, we need a paradigm shift in how we approach sepsis and similar critical illness syndromes, which moves us from prognosis to predictive biomarkers and trial enrichment.

Reframing sepsis

Accepting that clinical definitions of sepsis and sepsis immunobiology are largely disjunctive, Shankar-Hari et al. described a conceptual framework of the dysregulated host response from a biological perspective, defining dysregulation as ``*altered homoeostasis with pathological disruption of immune-driven resistance, disease tolerance, resilience and resolution mechanisms*´´ [7]. Immune resistance refers to functions of innate and adaptive immunity that act to reduce or eliminate pathogens but come at the cost of inflammation and tissue damage. These may be excessive (hyperinflammation) or depressed (immunosuppression). Disease tolerance describes host strategies that limit injury during infection but do not directly affect pathogen load, and resilience is the capacity of the immune system to rapidly restore homoeostasis at minimal inflammatory cost. Shankar-Hari et al. argue that thinking of the dysregulated response in terms of its component parts is necessary to develop predictive features and, by extension, to match appropriate treatments.

This is an important contribution. Until now, efforts to subtype sepsis have varied [8]. Some have pursued molecular subtypes, some clinical, and others combinations of the two. The biology underlying these subtypes is poorly

understood, as is the overlap between them [9]. Adopting a biological perspective, as outlined by Shankar-Hari et al., may enable a more accurate framing of sepsis subtypes based on the prevailing mechanism of dysregulation, which is in turn predictive of treatment response. To achieve this, we must move from concepts to causal pathways. There are multiple routes to this. Two are likely to become increasingly important: host genetics and deep phenotyping.

Host genetics

The influence of genetics on the risk of death from infection is more pronounced than in cancer or cardiovascular disease, highlighting the significant role host-genetic variation plays in sepsis [10]. Despite the interplay with environmental and pathogenic factors, genetic insights provide valuable opportunities for therapeutic development in sepsis.

Mendelian randomisation is one tool that leverages genetic variation to discern causative factors affecting sepsis outcomes. By using the random assignment of genotype at conception, Mendelian randomisation functions similarly to a randomised controlled trial in evaluating the impact of specific genetic variants on disease outcomes. This approach can assess the potential benefits of drugs by examining genetic variants that mimic the effect of a drug. For example, variations in the gene for the interleukin-6 (IL-6) receptor can simulate the effects of IL-6 receptor antagonists, such as tocilizumab. Studies using Mendelian randomisation suggest that certain IL-6 receptor variants reduce the risk of 28-day mortality in patients who are critically ill with sepsis, providing causal genetic evidence to support their use [11]. Mendelian randomisation also aids in distinguishing between associations and causal relationships. A notable example is the debated role of vitamin C in sepsis treatment. While patients with sepsis typically exhibit lower vitamin C levels, Mendelian randomisation studies have found no causal link between vitamin C levels and sepsis risk [12], a finding consistent with emerging trial evidence [13].

Genetic variation may provide clues to entirely new treatments for sepsis. The largest genome-wide association study of patients with critical illness, the Genetics of Mortality in Critical Illness (GenOMICC) study, was the first to identify an association between variants in the tyrosine kinase 2 gene and susceptibility to severe COVID-19 infection [14]. This finding led directly to the discovery of baricitinib as an effective treatment [15]. In future, the availability of large-scale genotype data, richly linked to clinical and biological phenotypes, will offer a means of dissecting the heterogeneity evident in sepsis.

Deep phenotyping

Beyond the genome, the emergence of increasingly sophisticated technologies is allowing us to characterise the epigenome, transcriptome, proteome, metabolome and microbiome at unprecedented resolution [16]. Data from these techniques permits deep immunophenotyping of the host response. Early efforts, using bulk transcriptomic signatures, identified a sepsis sub-phenotype with evidence of immunosuppression (SRS1) [17]; this signature was subsequently associated with a beneficial response to corticosteroid treatment in a previous randomised controlled trial [18]. More recently, using single-cell transcriptomic techniques, SRS1 has been shown to be associated with granulopoietic disturbances, specifically signal transducer and activator of transcription 3 (STAT3) driven emergency granulopoiesis [19]. Given that IL-6 signals via STAT3 participate in emergency granulopoiesis and are upregulated in SRS1, this work forms the foundation of an emerging sepsis endotype. In future, more of these studies will be required, including studies which integrate multiple layers of the host response (e.g. the transcriptome and the proteome) and which are longitudinal. Similarly, these techniques may allow us to pursue new therapeutic strategies. For example, epigenetic modifications (accumulated over time) are known to promote immunosenescence as we age [20], which in turn contributes to a higher risk of sepsis in older patients. A more detailed understanding of these mechanisms at play could point to targets amenable to an emerging class of epigenetic-modifying drugs [21].

Borrow to grow

Large-scale host-genetic and deep phenotyping efforts come with significant challenges; they are difficult to complete at scale, are costly and take time. We are also beginning from a place where much is unknown. Yet, it may be possible to expedite the discovery of actionable mechanisms in sepsis by borrowing from other sources. Perhaps the most obvious is COVID-19. In the first year of the pandemic, an estimated 1.5 million publications were added to the scientific literature [22]. Arguably, there is no human disease which we have characterised in more detail. This wealth of data provides an in-depth understanding of the host response, parts of which may overlap with the biological mechanisms underlying sepsis. Similarly, we know a great deal about many non-infectious inflammatory diseases, such as asthma and rheumatoid arthritis. Here, the overlap may be less but not zero. Crucially, these diseases have treatments, and while these conditions differ from sepsis, molecular or genetic traits may be shared with sepsis subtypes. Identifying these commonalities, by `transfer

learning´ from these well-studied areas to sepsis, may open new therapeutic avenues [23].

Syndromic agnosticism

Consider this scenario in ICU: a typical patient, without prior comorbidity, admitted to critical care with sepsis from a perforated bowel. In the next bed is a patient with acute respiratory distress syndrome due to pneumonia. While it is unlikely that the underlying causal mechanisms are identical, it is entirely plausible that some are shared and are susceptible to the same interventions [24]. These are treatable traits.

At its most proscriptive, a treatable trait is defined as a pathophysiologic feature implicated in the mechanism of disease, that determines whether a given intervention will modify outcome [25]. A more general definition relaxes the necessity for mechanism and may incorporate a group of features (e.g. a panel of biomarkers). Regardless, they are independent of clinical syndrome.

Studying interventions based on treatable traits removes the requirement for a syndrome. The TRAITS adaptive platform trial (https://traits-trial.ed.ac.uk) is one of the first examples of this approach in critical care. In this study, adult patients receiving organ support and with a SOFA score ≥ 2 are eligible for the platform. These individuals are then screened against trait-specific inclusion and exclusion criteria and randomised to treatment based on the presence or absence of these traits. So far, platform traits include `Lymp-Resp´ and `Endo-shock´. Endo-shock comprises acute circulatory failure and evidence of inflammation. Interventions in this trait will target mechanisms that modulate endothelial integrity such as imatinib, a tyrosine kinase inhibitor that inhibits the Abelson family of nonreceptor tyrosine kinases that mediate endothelial barrier function.

As our knowledge of the causal mechanisms underpinning the dysregulated immune response to infection, and even sterile injury, improves, it is likely that more (refined) traits will become evident. Many of these will contain targets amenable to therapeutic interventions.

If future meta-analyses of sepsis interventions are to look radically different from that of Robey et al. [3], then we will need new ways of thinking about sepsis immunobiology, new ways to unravel the molecular and genetic drivers, and new ways to deliver clinical trials. To paraphrase the words of the Anglo-Irish super-group Bananarama – sepsis: *``it ain't what you do, it's the way that you do it, that's what gets results!''*

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