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Evolving concepts in sepsis: we are making progress!

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An Editorial on the Frontiers in Science Lead Article

Deciphering sepsis: transforming diagnosis and treatment through systems immunology

Key points

- Sepsis is a complex dysregulated host response to infection, encompassing proinflammatory and immunosuppressive aspects that vary over time in the same patient while also differing from patient to patient.
- Better patient characterization using systems immunology approaches can help select patients for inclusion in trials of new therapeutic interventions and ultimately for more precisely targeted treatments.
- Greater collaboration among research scientists, clinicians, policymakers, and industry is needed to overcome the numerous challenges that remain as we transition toward a precision-medicine approach to sepsis treatment.

Sepsis, a word of Greek origin initially used by Hippocrates to refer to putrefaction, has become the term used to describe a serious infection, i.e., an infection complicated by organ dysfunction. The word sepsis is more appropriate than the term "septicemia", which has been widely used but implies the presence of microorganisms in the blood whereas blood cultures are positive in scarcely 50% of patients with sepsis.

Sepsis is a global disease responsible for some 20% of total annual deaths and designated as a worldwide health priority by the World Health Organization (1). It is difficult to estimate the full individual and societal burden of sepsis, especially as there are limited data available from low- and middle-income countries, yet these populations are likely to be disproportionately affected given the poorer access to good hygiene and poor resource availability for sepsis prevention and treatment in these areas (2). Moreover, in addition to its high mortality rates, sepsis is also responsible for considerable short- and long-term morbidity with an associated high economic impact in terms of costs of hospitalization and treatment, long-term care if needed, and lost workforce productivity. The impact of sepsis on the emotional, psychological, and social well-being of affected individuals and their families is also substantial. Recent initiatives such as the Global Sepsis Alliance (https://globalsepsisalliance.org), the

International Sepsis Forum (https://sepsisforum.org), and World Sepsis Day (https://www.worldsepsisday.org) have raised awareness of sepsis. Still, many challenges have yet to be addressed to reduce the huge burden of this condition worldwide.

The current management of sepsis relies on hemodynamic stabilization and infection control. Hemodynamic stabilization requires the administration of intravenous fluids, vasopressor agents (primarily norepinephrine and sometimes vasopressin), and inotropic agents (primarily dobutamine) when required. Infection control requires adequate antibiotic therapy and source control. Nevertheless, these measures are not, and will never be, fully effective. It is now recognized that not even the most effective antibiotic therapy can control all cases of sepsis. Being able to modulate the sepsis response is a tantalizing prospect but is currently limited to corticosteroid administration in severe cases and is a subject of ongoing debate and controversy (3).

The critical care community assumed for far too long that sepsis was a homogeneous, primarily hyperinflammatory host response to infection. This influenced our approach to developing potential therapies, leading us to focus on agents with anti-inflammatory or immunosuppressive effects. We now consider that the basic underlying mechanism is better described as a "dysregulation" of the host response (4). Understanding the different facets of this dysregulation will help in the development of more specific, targeted sepsis therapeutics.

These recent concepts and the possible systems immunology approaches that can be used to improve our understanding of the complexities of the sepsis response and thus move toward more precision-based treatments are beautifully presented by Hancock and colleagues in their lead article (5). There are some important aspects to remember. First, the underlying immune alterations of sepsis are highly complex and need to be better characterized in each individual patient: this is now becoming possible, especially with the assistance of artificial intelligence-based models. Second, these alterations can change rapidly over time, implying the need for regular, repeated assessments of the host response.

We can thus identify a path toward real progress in this field. After many years of negative trials trying to identify sepsis drugs that would be effective for *all* patients with sepsis, we have come to recognize that this was an oversimplistic illusion. Patients with sepsis are so different in terms of demographics, comorbidities, genetics, causative microorganisms, stage of disease at presentation, prior treatments, and degree of host response, among other factors, that identifying a single agent that would work for all was never going to be realistic. It has become obvious that more specific interventions are needed. Better characterization of individual patients will help determine which therapy is most likely to be of benefit to which patient. Hancock et al. (5) excellently describe some of the tools available to achieve this, focusing on endotypes, where patients are characterized according to underlying pathophysiological mechanisms, such as the degree or type of immune response. A recent roundtable conference held in Brussels proposed focusing also on patient subphenotypes or treatable traits, which characterize patients more according to specific clinical features or outcomes rather than biological mechanisms (6). The development of theranostics, combining diagnostic approaches (using biomarkers, endotypes, phenotypes, etc., to characterize patients) with appropriate therapeutic choices, has been used to guide the selection of the most relevant medication for individual patients in clinical trials in sepsis. For example, Vincent et al. selected only patients with sepsis-associated coagulopathy for inclusion in a randomized trial of thrombomodulin versus placebo (7), and Francois et al. assessed response to nangibotide, which modulates triggering receptor expressed on myeloid cells-1 (TREM-1), according to concentrations of soluble TREM-1—a known sepsis biomarker (8). It has even been suggested that we may no longer need the word "sepsis" to describe a patient's condition and should find a replacement using methods that more precisely evaluate and define the immune status.

Nevertheless, several hurdles remain. One is that a patient's characteristics may change rapidly over time, and the trend is not predictable or identical for everyone. The specific moment of onset of sepsis is also generally not known with precision; sepsis may have developed before admission to the intensive care unit (ICU) or even before admission to the hospital. Second, different types of response may coexist: some cells may be in a hyperinflammatory state at the same time as others are immunosuppressed (9). Third, we usually assess the host response in the blood, but any alterations may be different in the tissues. To overcome some of these challenges, new studies need to investigate not only mortality outcomes but also other patient-relevant benefits, including limiting the development of organ failure and facilitating an uncomplicated recovery with shorter ICU and hospital stays. Even if a therapeutic strategy is not demonstrated to increase survival, effects on other outcomes can be clinically meaningful. Trial designs other than the traditional randomized controlled trial may also help in identifying and assessing new interventions (6). Adaptive clinical trial designs, for example, initially include multiple trial arms, and those showing promise are continued while others are rapidly discontinued. With the improved patient characterization methods highlighted by Hancock et al. (5), clinical trials could also focus not so much on the presence of an infection, which is sometimes difficult to establish definitely (10), but on a particular pattern, characterized by a specific marker, endotype, phenotype, and so on. So-called "basket trials" are now used in oncology to test whether a new drug can be effective in patients who have a certain abnormality regardless of the type of cancer. Likewise, critically ill patients could be enrolled in a trial when they have a particular profile, regardless of the documented presence of infection.

As new therapies become available through these novel approaches, a reasonable management option, based on current knowledge, may be to initially use an intervention that could reduce the inflammatory response when present and then immunostimulate the host in the later phase of immunosuppression. Limitations to this approach are that the proinflammatory response may be quite short (11), the two phases may be present simultaneously in some patients, and the immunosuppressive phase may not contribute markedly to mortality (12). The better characterization of patients that is now becoming possible, as Hancock et al. (5) have discussed, will facilitate appropriate treatment choices for individual patients.

In conclusion, better characterization of the host response over time in individual patients with sepsis will help advance research in this field, allowing potential therapies to be trialed in more precisely defined populations who are most likely to benefit. This will enable

the host response to be controlled more precisely and thus more effectively. Global collaboration of multiple stakeholders—research scientists, clinicians, industry, healthcare managers, politicians, and governments—is needed to help overcome the remaining challenges and obstacles, including the high associated costs, and drive the incorporation of precision medicine into clinical practice to help improve sepsis outcomes.

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