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EDITORIAL

"What's new?"

Immunostimulating strategies in the ICU

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Introduction

Until now, treatment of sepsis has been characterized by two revolutionary steps that significantly improved survival: the introduction of antibiotics and the development of intensive care units (ICUs). Whereas antibiotics target the pathogen, all other treatments focus on *support* of the host. As sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to an infection [1], a third revolution—immunotherapy *targeting* the patient's immune reaction—might be at the break of dawn to further improve the outcome of sepsis patients.

Previously, immunotherapy for sepsis completely focused on attenuation of the immune response, e.g., by employing pharmacological inhibition of lipopolysaccharide, Toll-like receptor 4 signaling, or pro-inflammatory cytokines [2]. Without exceptions, these attempts have been unsuccessful, plausibly related to ignorance pertaining to the heterogeneity of the immune response in sepsis and failure to stratify patients on the basis of their current immune status. Patient selection was merely based on severity of disease, resulting in *prognostic* enrichment: patients expected to have a high event rate (e.g., 28-day mortality) were selected. However, this does not take into account the likelihood of success of the immunomodulatory treatment under investigation, as this depends on the specifics of the host response of that patient [3]. Biological plausibility leads to *predictive* enrichment and increases the chances to demonstrate clinical efficacy.

Activation of both pro- and anti-inflammatory immune responses occurs promptly after sepsis onset. While overzealous inflammation may indeed be responsible for "collateral" organ damage, we now know that sepsis-induced immunoparalysis also contributes to mortality. Emerging techniques allow us to chart the hosts' genome, epigenome, transcriptome, and metabolome. This multi-layered *omics*-based immunoprofiling will provide detailed information to facilitate novel precision immunotherapies in sepsis. For example, patients with sepsis admitted to the ICU can be subdivided in so-called endotypes with pathophysiologic and prognostic implications based on their blood leukocyte gene expression profiles [4, 5]. The signaling pathways that emerged are relevant to the innate and adaptive immune system. Because a patient with a certain endotype displays higher expression of genes corresponding to a specific signaling pathway, it is biologically plausible that they are more likely to respond to a treatment aimed at this pathway. Analyses limited to neutrophil CD88, HLA-DR and percentage of regulatory T cells as markers of immune dysfunction illustrated a progressive increase in risk of secondary infections from 14% of ICU patients with no immune dysfunction to 59% with dysregulation of all three markers [6]. Of interest, a combination of prognostic and predictive strategies based on serum protein and messenger RNA biomarkers could identify a subgroup of children with septic shock that may be more likely to benefit from corticosteroids [7], illustrating the validity of predictive enrichment.

Immunostimulatory compounds

Several immuno-adjuvant agents are under investigation, including granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), anti-programmed death-ligand 1 (anti-PD-L1), and interleukin-7 (IL-7). GM-CSF and IFN-γ are potent enhancers of myeloid cell function. A biomarker-guided randomized controlled trial (mHLA-DR < 8000 monoclonal antibodies/

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cell) showed that GM-CSF was effective in restoring monocytic immunocompetence and appeared to be associated with beneficial clinical outcomes [8]. IFN-γ showed promising results in several small case series [9], and a randomized controlled trial is currently being conducted (NCT03332225). Blockade of PD-1 pathway represents another promising strategy. These antibodies are known as checkpoint inhibitors, because they stop potentially autoreactive T cells at the initial or priming stage of naive T cell activation. A phase 1b trial with anti-PD-L1 (NCT02576457) in 24 sepsis patients yielded no unexpected safety findings. Immune restoration at higher dosages was evidenced by a trend toward increased mHLA-DR expression over time (personal communication, Professor R. Hotchkiss). Unfortunately, a large multicenter trial was recently aborted by the sponsor because of other priorities. IL-7 is an anti-apoptotic cytokine that is essential for lymphocyte proliferation and survival. IL-7 increases the number and function of CD4 helper T cells, and was found to exert a broad and long-lasting effect on immunity, while no safety issues emerged in a phase 2 trial in 27 patients with septic shock and lymphopenia [10]. To what extent the described effects translate into clinical benefit for sepsis patients needs to be determined.

Other patient groups in the ICU

The development of immunoparalysis does not exclusively occur in sepsis patients. It has become clear that not only pathogen-associated molecular patterns (PAMPs) but also danger-associated molecular patterns (DAMPs) induce immunosuppressive effects. In multiple trauma patients, increased levels of DAMPs, related to cytokine responses and decreased HLA-DR expression, were shown to be associated with the development of secondary infections [11]. Similarly, release of DAMPs following cardiac arrest is associated with

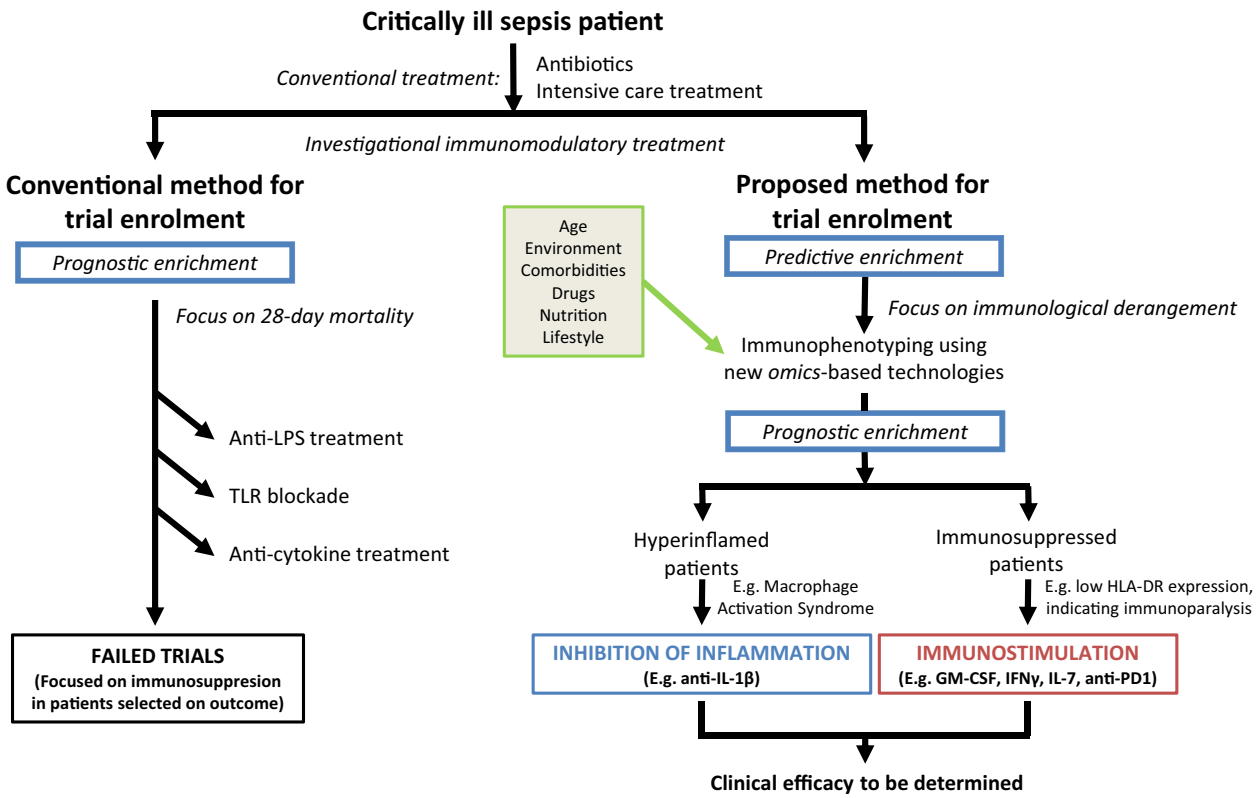

Fig. 1 Displaying the current therapy and the conventional and proposed method to approach new investigational immunomodulatory treatment. The conventional methodology to investigate new compounds is to apply inclusion and exclusion criteria aimed to select a patient group with focus on mortality, called *prognostic* enrichment. Biological plausibility for the new compound to exert therapeutic efficacy is not taken into account. Trials that used this methodology did not show therapeutic efficacy of the compounds tested, e.g., IL1-receptor blocker anakinra [14]. If immunophenotyping is used to select patients, e.g., with an overactive but ineffective immune response, for example macrophage activation syndrome, IL-1 pathway inhibition might exert therapeutic efficacy [15]. In another subgroup of patients with a suppressed immune system, immunostimulatory therapies appear more likely to improve the outcome of the patient. Secondary to this so-called *predictive* enrichment, prognostic enrichment could still be applied if it is desired to select patients, e.g., with a high risk of dying

the development of immunoparalysis [12], which may explain the increased susceptibility of these patients toward infections. The combined observations that infections in these patient groups are related to immunoparalysis and importantly contribute to long-term mortality suggest that immunostimulatory therapy might represent a treatment possibility for these patients as well (Fig. 1).

In conclusion, it is clear that a patient-tailored approach in sepsis treatment is required and that complementary knowledge of host–pathogen interactions and cutting-edge *omics*-based technologies represent promising tools to do so. Immunostimulatory therapies may represent a viable adjuvant strategy for the treatment of immunoparalyzed patients, which has the potential to represent a qualitative leap for the prognosis of sepsis, as well as other immunoparalyzed patient groups. Importantly, new studies aiming to reverse immunoparalysis should not employ a "one size fits all" strategy, as a recent observational study shows that secondary infections are responsible for only 10% of overall sepsis mortality in the ICU [13], raising doubt about the potential impact of immune stimulation in unselected sepsis populations. Clearly, as both hyperinflammation and immunoparalysis are of importance in sepsis, it is appreciated that they are present in individual sepsis patients to a different and time-dependent extent. Clinical benefit of immunomodulatory therapies needs to be established, arguably using reduction in secondary infections and/or improved long-term morbidity as additional endpoints besides mortality. In view of the lack of positive results following inhibition of inflammation in unselected sepsis patients, the only way to break this deadlock is by applying a precision medicine approach, which may well spark a third revolution.

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Compliance with ethical standards

Conflicts of interest
TvdP has no conflicts of interest with relevance for this manuscript. PP has no conflicts of interest with relevance for this manuscript.

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