Evangelos J. Giamarellos-Bourboulis, JAMA. 2025 Dec 8.

Precision Immunotherapy to Improve Sepsis Outcomes – The ImmunoSep Randomized Clinical Trial

BACKGROUND

The optimal resuscitation strategy for patients with septic shock remains uncertain.

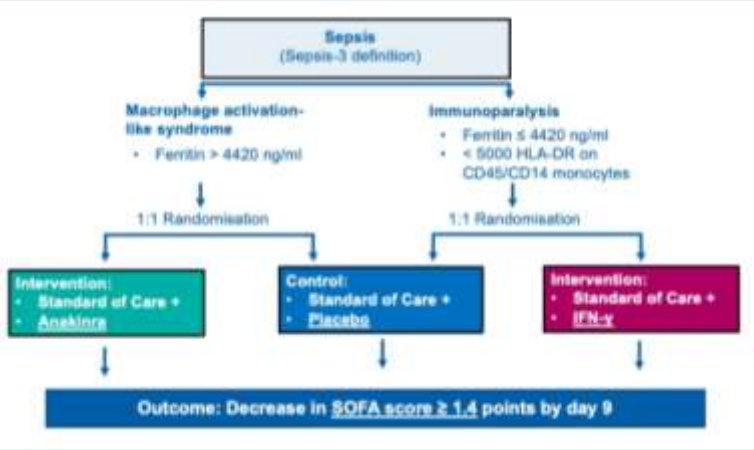
RESEARCH AIM

To evaluate whether precision immunotherapy targeting:
- **macrophage-like syndrome (MALS) and**
- **immunoparalysis**

improves organ dysfunction in sepsis.

METHODS

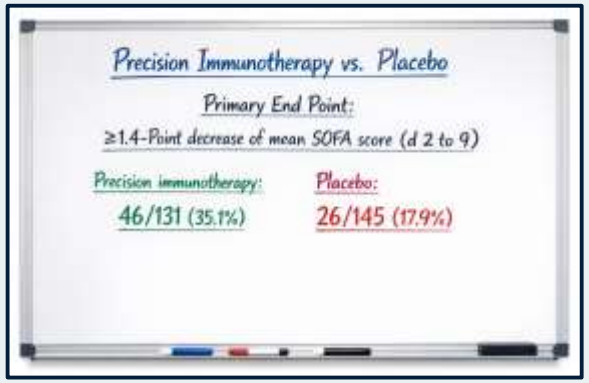
Design:
- International, multicentric randomized trial including adult patients with septic shock



Results

Patients:
- 267 patients with septic shock
- 33 sites in 6 countries
- Intervention group:
  - MALS: 19.1% (25/131)
  - Immunoparalysis: 80.9% (106/131)
- Placebo group:
  - MALS: 15.9% (23/131)
  - Immunoparalysis: 84.1% (122/131)

Primary endpoint:



Fisher exact test - p-value 0.002
OR: 2.48, 95% CI 1.42-4.32

Secondary endpoints:

	Precision Immunotherapy	Placebo	P
28-d mortality	43.5%	49.7%	0.34
90-d mortality	68.7%	67.6%	0.9

Reduction of SOFA score ≥ 1.4 by subgroups

	Precision Immunotherapy	Placebo	p
MALS	48.0%	17.4%	0.04
Immuno paralysis	32.1%	18.0%	0.02

CONCLUSION

- **In septic patients, immunoparalysis,** measured by reduced HLA-DR expression on monocytes, **occurs more frequently than MALS,** identified by elevated ferritin levels.
- **Precision immunotherapy with Anakinra or IFN-γ**, targeting MALS and septic immunoparalysis, **improves organ dysfunction** by day 9.

SIS COMMENTS

A new era of individualised immunomodulation in sepsis

Since Hippocrates first introduced the term ”sepsis” into medical discourse, describing a pathological state characterised by rotting or putrefaction of bodily humours, its definition has evolved substantially. Despite these changes, one central concept remained consistent for centuries. From Hippocrates through Galen and later Semmelweis, Pasteur, and Koch, sepsis was understood as a systemic process leading to progressive deterioration of bodily function. It was only in the nineteenth century that this process was attributed to microorganisms. Subsequently, in the late twentieth and early twenty-first centuries, a broader conceptual shift occurred, recognising sepsis as a dysregulated systemic response of the host to infection, ultimately resulting in multiorgan dysfunction or failure [1,2].

As the conceptual understanding of sepsis advanced, therapeutic strategies evolved accordingly, leading to extensive investigation of immunomodulatory approaches aimed at directly targeting this dysregulated host response. Based on the long-standing assumption that sepsis is accompanied by a predominantly hyperinflammatory state, a wide range of clinical trials have been conducted with the goal of suppressing the inflammatory burden. These efforts span early trials using monoclonal antibodies targeting bacterial endotoxins, through inhibition of specific cytokines and their receptors, broader immunosuppression with corticosteroids, and more recent approaches focusing on endotoxin and cytokine removal. Collectively, however, these trials have demonstrated limited or no clinically relevant benefit.
Roger C. Bone was among the first to describe sepsis not only as a pro-inflammatory burden, but as a process characterised by a systemic inflammatory response accompanied by a compensatory anti-inflammatory process. He further hypothesised that the failure of previous anti-inflammatory trials might be explained by the existence of distinct immunological phases of sepsis, thereby opening a new era of patient phenotypisation aimed at distinguishing hyperinflammatory from hypoinflammatory states [3].

Building on this concept, Evangelos J. Giamarellos-Bourboulis used a biomarker-based stratification in their ImmunoSep trial, to distinguish patients with features of macrophage activation-like syndrome (MALS), indicated by high ferritin levels, from patients with sepsis-associated immunoparalysis characterised by low HLA-DR expression [4]. By selectively treating patients with MALS using the IL-1 receptor antagonist anakinra, and patients with sepsis-associated immunoparalysis with interferon-γ, a faster improvement in multiorgan failure by day 9 was achieved compared with standard of care.

This study has several highly relevant aspects:
First, by applying a simple form of phenotypisation based on only two biomarkers, the investigators demonstrated that targeted treatment with corresponding immunomodulatory agents resulted in improvement in organdysfunction in both interventional arms. Notably, a substantially larger proportion of patients could be allocated to the immunoparalysis group, providing strong support for Bone’s original hypothesis that impaired immune function contributes to a significant proportion of sepsis cases in critical care and may represent a major reason for the failure of previous broadly applied anti-inflammatory trials.

A second important aspect relates to the clinical relevance of outcomes in this patient population. In this international study encompassing six European countries, 28-day mortality ranged between 40% and 50%. At 90 days, however, mortality exceeded 60% in both treatment groups, without evidence of a beneficial trend associated with any of the investigated interventions. These findings highlight the severity of illness in the studied cohort and underscore the urgent need for more effective therapeutic strategies that prioritise improvements in patient-centred, long-term outcome measures.

The third aspect relates to the limitations of the proposed phenotypisation algorithm. Despite its elegance and simplicity, more than half of all screened patients (391 of 672) could not be included because they could not be allocated to either immune phenotype based on the predefined thresholds for ferritin and monocyte HLA-DR expression. It is unlikely that these patients lacked relevant immune alterations compared with non-septic patients. This underscores rather the need for more refined definitions and additional biomarkers to more accurately identify, stratify, and treat patients according to their immunological state.

In summary, this work represents a substantial step towards the advancement of precision medicine in sepsis, demonstrating that biomarker-guided, precision-targeted immunomodulation can achieve measurable clinical effects. However, further efforts are required to improve the reliability and bedside applicability of immunological phenotyping in sepsis, in order to tailor phenotype-specific therapies with sustained impact on long-term outcomes.

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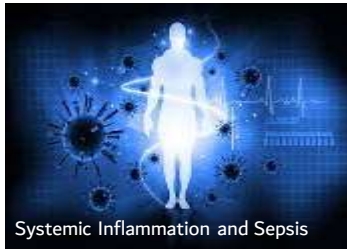

1. Bone, Chest 1992
2. Singer, JAMA 2016
3. Bone, JAMA, 1996
4. Giamarellos-Bourboulis, JAMA, 2025

Mattia M. Müller & Sascha David for the SIS section