Novel Interventions
What's New and the Future

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KEYWORDS

• Septic shock • Microcirculation • Interferon • Thrombomodulin
• Immunosuppression • Personalization • Biomarkers • Organ dysfunction

KEY POINTS

- Rather than testing new interventions in poorly characterized patient populations, the current trend is to study interventions in well-defined patient populations characterized by a special feature or a particular biomarker.
- The current focus is on immunomodulation in a broader sense rather than on only antiinflammatory strategies or strategies designed to improve the host response.
- Improving endothelial cell function, blood purification and immunostimulation are important areas of current research in sepsis therapeutics.

INTRODUCTION

Despite several decades of sepsis research, no specific therapies for sepsis have emerged and current management still relies on source control, antibiotics, and organ support. One of the reasons for the many failed trials of potential new interventions has been the lack of clear patient inclusion criteria, resulting in heterogeneous populations unlikely to all respond positively to the intervention in question. As the understanding of sepsis pathophysiology continues to improve and new techniques are developed to help better characterize patients with sepsis, particularly in terms of their immune status, clinical trials are beginning to better target new interventions at those patients most likely to respond, rather than at the poorly characterized heterogeneous groups of patients widely used in the past. Biomarkers are also being used to identify groups of patients most likely to respond to specific therapies.

Given the complexity of sepsis, there are almost limitless potential avenues for novel therapeutic agents, but this article concentrates on 3 of the most important current trends that show promise:

- Decreasing harmful capillary leak and edema formation by protecting or restoring endothelial cell function

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- Reversing sepsis-induced immunosuppression by immunostimulation
- Removal of harmful mediators from the blood using extracorporeal techniques

PHARMACOLOGIC TREATMENT OPTIONS

Endothelial Cell Protection

Disturbed endothelial function plays a key role in the development of sepsis and associated organ dysfunction, partly as a result of altered endothelial permeability leading to edema formation. Several potential therapies have been developed that have endothelial cell protective functions, including vasopressin, interferon (IFN)-beta, and thrombomodulin.

Vasopressin

Patients with septic shock are said to have a relative deficiency of vasopressin,[1] hence the rationale for using exogenous arginine vasopressin (AVP) as an adjunct therapy in these patients. Several studies using AVP in conjunction with catecholamines have shown that AVP administration enables doses of catecholamines to be reduced.[2] This finding is not surprising. The question is whether the use of vasopressin is associated with better outcomes, and this has not been shown.[3,4] Therefore the latest Surviving Sepsis Campaign guidelines do not make any specific recommendation about the use of vasopressin in septic shock.

Vasopressin acts via 3 specific receptors: in addition to its V1A receptor–mediated vasopressor actions, its actions on other receptors, including V2 and oxytocin receptors, may aggravate sepsis-induced vasodilation and promote fluid accumulation. Therefore, AVP analogues that are highly specific for the V1A receptor and may thus avoid the potentially negative effects of AVP mediated via other receptors have been developed. Selepressin is one of these substances, and its use was shown to reduce vascular leak in an ovine model of pneumonia-induced sepsis.[5] In an ovine model of peritonitis-induced septic shock, selepressin use was associated with better hemodynamic stabilization, preserved lung and renal function, reduced cumulative fluid balance, and prolonged survival, particularly when given early in the course of shock.[6] In a small randomized controlled trial, 50 patients with septic shock were randomized to receive selepressin 1.25 ng/kg/min, selepressin 2.5 ng/kg/min, or placebo. The results suggested a dose-dependent reduction in norepinephrine requirements, reduced need for mechanical ventilation, and shorter time to shock resolution.[7] In view of these encouraging data, a larger clinical trial, targeting 1800 patients, is now ongoing (Selepressin Evaluation Program for Sepsis-Induced Shock - Adaptive Clinical Trial [SEPSIS-ACT]; ClinicalTrials.gov identifier, NCT02508649) in which patients with vasopressor-dependent septic shock are randomized to receive 1 of 4 doses of selepressin or placebo. This study will use an adaptive clinical trial design, which will enable enrollment in nonpromising treatment arms to be stopped during the course of the study, so improving the study efficiency. The primary end point is a composite of 30-day vasopressor-free and mechanical ventilator–free days.

Interferon-beta

Adenosine is an extracellular signaling molecule that regulates multiple immunologic processes and is thought to play an important role in regulating the host response to sepsis.[8] Inhibition of adenosine deaminase was associated with reduced vascular leakage and improved survival in septic mice.[9] Cluster of differentiation 73 (CD73) is a cell surface enzyme that catalyzes the dephosphorylation of soluble AMP into adenosine, and is upregulated by IFN-β.[10,11] IFN-β may, therefore, help restore endothelial integrity by increasing local adenosine levels. IFN-β may also upregulate silent