# Modulation of Severe Immune Dysregulation in Sepsis and ARDS Using Apoptotic Cell Therapy

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Sepsis currently lacks a proven targeted pharmacologic therapy beyond standard supportive care, which includes appropriate antimicrobial agents, fluid resuscitation, vasopressor support as needed, and, in selected cases, corticosteroids. The condition is primarily initiated through the concurrent recognition of pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) by components of the innate immune system.
In both murine and human sepsis studies we used successfully reprogramming of macrophages by apoptotic cells. We utilized the murine cecal ligation and puncture (CLP) model of sepsis to investigate the effects of post-CLP infusion of apoptotic cells (Allocetra-OTS) in a severe sepsis setting. Comprehensive assessments included cardiovascular function, acute kidney injury (AKI), acute liver injury (ALI), as well as hematologic and metabolic parameters. Cytokine and chemokine profiles were quantified using multiplex ELISA, while mitochondrial function and glycolytic activity were evaluated using Seahorse analysis. Disease severity was determined using the Murine Sepsis Score (MSS).
CLP-induced sepsis in mice was characterized by hypotension, reduced cardiac output, pulmonary dysfunction, AKI, ALI, and thrombocytopenia. These findings correlated with MSS values and were associated with a pronounced cytokine and chemokine storm. Administration of apoptotic cells significantly attenuated this hyperinflammatory response, restored mitochondrial and glycolytic function in leukocytes, and led to a marked improvement in survival (from 6% to 60%, $P < 0.0001$), alongside significant amelioration of organ dysfunction.
Consistent with these findings, treatment of 21 patients with severe acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 infection, as well as over 60 patients with sepsis, using Allocetra-OTS to induce macrophage reprogramming resulted in notable clinical improvement.
In conclusion, these findings suggest that the dysregulated immune response characteristic of severe infectious conditions can be effectively modulated through the administration of apoptotic cells.