



## Mesenchymal Stem Cell Therapy for Severe Sepsis and Septic Shock

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Sepsis is a serious and life-threatening clinical syndrome resulting in tissue perfusion disorder and can lead to organ dysfunction, shock, and even death. Although the rate of mortality is still high (30%–70%), it is associated with half of all in-hospital deaths. It is also one of the high cost diseases worldwide.

The host immune response to the infection is critical. Although early-phase sepsis is characterized by a hyper-inflammatory immune response, the later phase of sepsis is often complicated by suppression (1, 2). Continuous developments have been achieved in understanding the pathogenesis, and the treatment of sepsis has also clearly improved in the last four decades; however, no specific sepsis therapy exists. Currently, principles of sepsis management are based on the following points: early diagnosis and prompt initiation of sepsis management, severity of sepsis, etiologic diagnosis, effective antimicrobial therapy, source control, maintain tissue perfusion/oxygenation and preserve organ function, and prevent complications during/following the episode of severe sepsis. Sepsis is a medical emergency and therefore, when sepsis is suspected, antimicrobial treatment should be initiated within the first one hour. Antibiotic resistance is also a growing problem worldwide. A limited number of antibiotics such as colistin and carbapenem are useful in treating resistant bacterial infections. Moreover, it seems that there will be no new antibiotics in the near future for clinical use (2–4).

Although there are no therapies directing to modify the pathophysiology and injury mechanisms of sepsis, supportive management remains crucial. Studies over the last four decades have been focused on suppressing the early proinflammatory response to sepsis. To date, more than 40 unsuccessful clinical trials have been reported for agents that reduce pathogen recognition and/or block proinflammatory cytokines and/or inflammation-signaling pathways in sepsis (3, 4).

Recently, murine models of sepsis have increasingly been used because of their lower cost, shorter generation time, ease of housing and care, easier application methods, and the presence of transgenic species (5). The experimental murine models of sepsis are broadly divided into three categories: host barrier disruption models (including cecal ligation and incision, cecal ligation and puncture, and colon ascendant stent peritonitis), exogenous administration of a viable pathogen (*Escherichia coli*, *Staphylococcus aureus*, etc.) and administration of a bacterial toxin (LPS, lipoteichoic acid, peptidoglycan, zymosan, etc.). Especially in recent years, extensive use of broad-spectrum antibiotics has resulted in the emergence of multiple drug resistant nosocomial agents, and this has made the treatment of infections difficult (6). Moreover, in the absence of a new antibiotic, alternative treatment options have emerged. Therefore, the use of mono or combined therapy including available antibiotics or cellular therapy for the treatment of sepsis has been brought to the agenda (6). In addition, stem cells may be an emerging candidate for treatment of sepsis and can be considered as an alternative therapeutic approach.

Mesenchymal stem or stromal cells (MSCs) are adult cell population with self-renewal ability and are multipotent (7). They express cluster of differentiation (CD) 73, CD90, and CD105 surface markers while lacking CD34 and CD45, which are related to hematopoietic cell expression (7). Bone-marrow, umbilical Wharton jelly tissue, dental tissues, adipose or fat tissue, skin/foreskin, and several tissues may be sources of MSCs (8–13). MSCs have immunoregulation and tissue-repair roles beside their antimicrobial capacities (9–15). Mei et al. reported the direct bactericidal activity of MSCs is due to increased bacterial phagocytosis by macrophages (9). MSCs can produce antibacterial agents such as prostaglandin E2 (10) and LL-37 peptide (11). Efficacy of MSCs against gram-negative and -positive organisms related to bacterial pneumonia (12) and its antiviral effect in (13) preclinical models have been reported. The immune-modulatory factors including interleukin-10 (IL-10), IL-1, IL-6, leukocyte inhibitory factor (Lif), prostaglandin E2, and hepatocyte growth factors which are secreted by MSCs may limit immune responses. Moreover, MSCs are involved in the maturation of immune cell populations that results in increased number of regulatory T cells, anti-inflammatory T helper II cells, second subgroup of dendritic cells (DC) and an-

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ti-inflammatory M2 macrophages, whereas number of proinflammatory T helper I cells, first subgroup of DCs, natural killer cells decreases; moreover, MSCs reduce IgG production from B cells (14). MSCs may enhance tissue repair and restoration after sepsis and restore endothelial barrier function, which is mediated, partly, by secretion of factors that enhance resolution of tissue injury (15).

The immunosuppression and immunomodulation properties of MSCs are desirable and have been evaluated in a wide spectrum of clinical studies. MSC therapy offers a promising treatment option for several conditions including autoimmune diseases, heart diseases, and transplant surgeries over the past 25 years. The results of these cell application procedures have exhibited an excellent safety profile (14). Recently, over 1043 clinical trials involving MSCs have been planned for different indications and were registered in [clinicaltrials.gov](http://clinicaltrials.gov), these clinical trials enrolled 47,548 patients (14); however, of these only six clinical trials were assessed the effect of MSCs on sepsis or septic shock (2).

Preclinical studies have demonstrated the potential of MSCs for sepsis therapy (9–13). The MSCs' mechanisms of actions have been increasingly well characterized *in vitro* and in preclinical studies that include modulation of the immune cell response, reduction of host injury from the proinflammatory response while augmenting bacterial clearance by indirect and direct mechanisms of action, and enhanced resolution of inflammation and enhanced tissue repair after injury (14). Although there have been limited clinical trials, initial reports are encouraging. However, considerable barriers relating to sepsis and MSCs as a treatment exists that significantly impede the clinical translation of MSCs for treatment of patients with sepsis, which needs to be overcome if the therapeutic potential of MSCs is to be realized.

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