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Mesenchymal stem/stromal cells as a therapeutic for sepsis: a review on where do we stand?

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Abstract

Sepsis is one of the leading causes of morbidity and mortality in the United States and Worldwide despite advances in quick recognition and early antibiotics, fluids, and vasopressors. Mesenchymal stem/stromal cells (MSCs) have gained attention as a biologic therapy given their unique anti-inflammatory, immunomodulatory, and anti-bacterial characteristics. MSCs have had success in treating a range of diseases, however limited clinical trials exist specifically for MSC use in sepsis. This article reviews the properties of MSCs that make them favorable for treating sepsis, as well as the current state of clinical trials. All clinical trials presented here demonstrated MSC safety, with a mixture of efficacy results and a heterogeneity of trial methods. Ultimately, MSCs are a promising novel therapeutic for sepsis, however a consensus in cell source, dosage, preparation, and delivery needs to be further investigated for MSCs to transition from bench to bedside and become a true therapeutic for sepsis.

Keywords Sepsis, Septic shock, Mesenchymal stem cells, MSC, Clinical trials

Introduction

Sepsis is one of the leading causes of morbidity and mortality in the United States and Worldwide with traditional therapies resulting in a 15–50% mortality rate [1]. Sepsis is characterized by a robust and uncontrollable immune and inflammatory response [2]. This uncontrollable response leads to life-threatening organ dysfunction, damage, and death. Current treatment for sepsis revolves around rapid antibiotic initiation, fluid resuscitation, lung-protection strategies, glucose management, and vasopressor support [3]. Currently, there are no drugs approved for the treatment of sepsis, and the majority of clinical trials with novel therapies have been unsuccessful in reducing mortality [2].

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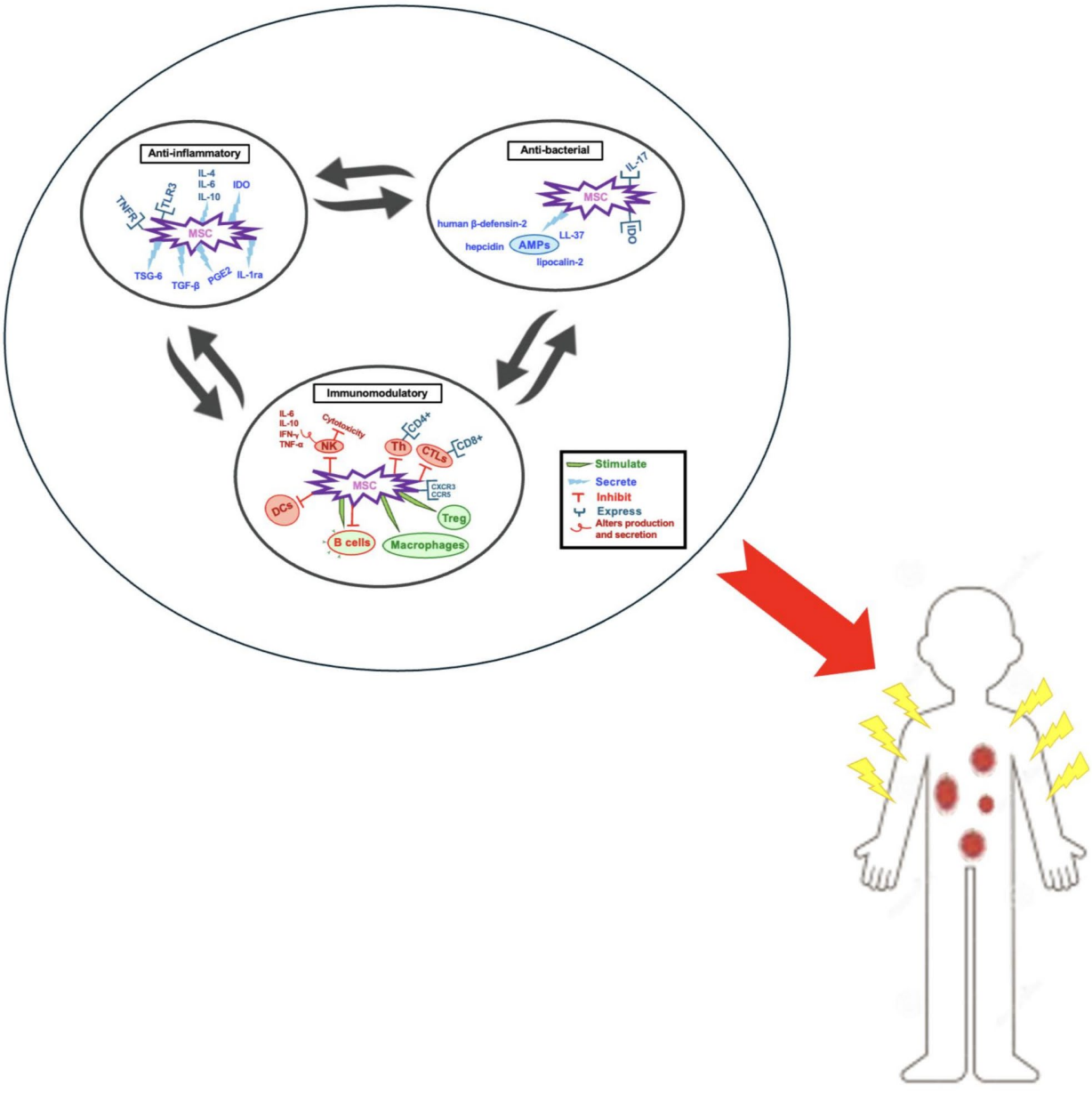
Mesenchymal stem/stromal cells (MSCs) have a unique therapeutic potential due to their anti-inflammatory, anti-bacterial, and immunomodulatory effects [4]. In preclinical models, MSCs have been shown to have a significant mortality benefit in animals with induced sepsis [5]. In limited clinical trials, MSCs have demonstrated safety and efficacy [6–11].

In this review, we outline the properties of MSCs that give them their unique advantage as a therapeutic for sepsis. Additionally, we investigate the current clinical trials utilizing MSCs in sepsis and discuss the limitations of MSC use in sepsis.

Methods

This review provides an evaluation of the use of MSCs in sepsis. Clinical trials were identified through Cochrane library and clinicaltrials.gov using the keywords "mesenchymal stem cells" and "sepsis" and "clinical trials." All clinical trials with MSCs targeting sepsis were included

Graphical abstract



in this review, irrespective of active ongoing trials, unknown status, or no published results. The investigators extracted clinically relevant data from included studies, including cell source, cell preparation, injection numbers, trials results and subsequently summarized and analyzed into a concise review. COVID-19 and ARDS specific trials were excluded since patients were not divided as septic versus non-septic.

Mesenchymal stem/stromal cells

MSCs are non-hematopoietic multipotent adult stem cells that have the capacity to differentiate into multiple lineages including mesodermal (osteoblasts, chondrocytes, and adipocytes), endodermal (hepatocytes), and ectodermal (neurocytes) [12]. MSCs express an array of cell surface markers; they are most commonly isolated via the expression of CD105, CD90, and CD73 and the absence of CD45, CD34, CD14, CD19, CD11b, CD79a, and HLA-DR. MSCs are also identified by their ability to adhere to plastic in standard culture condition [12]. Since

initial discovery in the late 1960s, MSCs have demonstrated numerous biological roles including multilineage differentiation, immunomodulation, immunoregulation, anti-inflammatory activity, anti-fibrotic activity, pro-angiogenic activity, angiogenesis, chemo-attraction, and tissue repair [12, 15, 16, 27, 28].

Essential properties of MSCs that make them a promising therapeutic for treating sepsis

MSCs have gained attention as a novel therapeutic for a myriad of disease processes by virtue of their unique properties [4]. Importantly, MSCs are anti-inflammatory and anti-fibrotic, immunoregulatory, anti-bacterial, pro-angiogenic, and importantly have low-immunogenicity [13]. Given sepsis is triggered by a robust and dysregulated immune response, MSCs hold significant promise as a therapeutic due to the dynamic interplay between their anti-inflammatory, anti-bacterial, and immunomodulatory mechanism of action (Fig. 1).

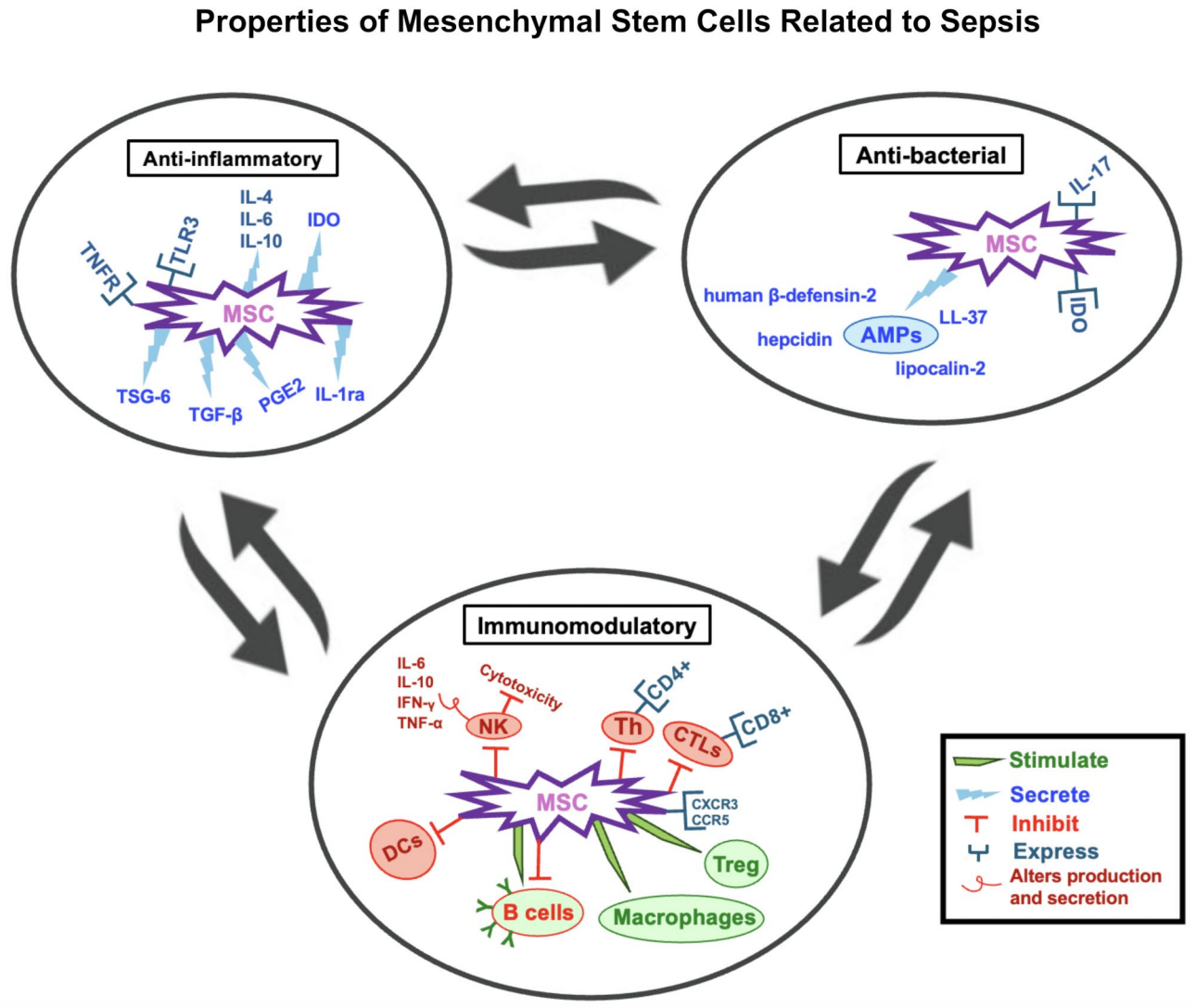


Fig. 1 Unique properties of mesenchymal stem cells (MSCs) that make them applicable for therapeutic use in sepsis. MSCs exhibit dynamic anti-inflammatory, immunomodulatory, and anti-bacterial properties that work synchronously. Their anti-inflammatory properties rely on the expression of tumor necrosis factor receptor (TNFR), toll-like receptor 3 (TLR3) and the secretion of interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), indoleamine 2,3-dioxygenase (IDO), tumor necrosis factor-stimulated gene-6 (TSG-6), transforming growth factor beta (TGF-β), prostaglandin E2 (PGE2), and interleukin 1 receptor antagonist (IL-1ra). Their immunomodulatory properties rely on the inhibition of dendritic cells (DCs), natural killer (NK) cells, CD4 + T helper (Th) cells, CD8 + cytotoxic T cells (CTLs), inhibition and stimulation of B cells, stimulation of macrophages and T regulatory (Treg) cells. Specifically, inhibition of NK cells results in inhibition of cytotoxicity and alteration in production and secretion of IL-6, IL-10, Interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α). Their anti-bacterial properties rely on the expression of IDO and interleukin-17 (IL-17) and the secretion of antimicrobial peptides (AMPs) including human β -defensin-2, hepcidin, LL-37, and liocalin-2

Anti-inflammatory properties

MSCs attenuate inflammation in response to pro-inflammatory cytokines such as interleukin-1 beta (IL-1β) and interferon gamma (IFN-γ), as well as activation via tumor necrosis factor receptor (TNFR) and toll-like receptor 3 (TLR3) [14, 15]. This in turn leads to a cascade of immunomodulatory effects including modulating T cells, natural killer (NK) cells, and B cells and anti-inflammatory effects [16]. Specifically, MSCs activated by TLR3 and TNFR2 secrete anti-inflammatory cytokines such as transforming growth factor beta (TGF-β) and interleukin-10 (IL-10) [17, 18]. Additionally, this cascade leads to MSCs secretion of tumor necrosis factor-stimulated gene-6 (TSG-6), prostaglandin E2 (PGE2), interleukin 1 receptor antagonist (IL-1ra), and indoleamine 2,3-dioxygenase (IDO) that are crucial for their inflammation modulation [16, 19].

While MSCs have been shown to secrete numerous cytokines, interleukin-4 (IL-4), interleukin-6 (IL-6), and interleukin-10 (IL-10) play critical roles in their anti-inflammatory response. IL-4 has been shown to hamper inflammation by converting pro-inflammatory M1 macrophages into an anti-inflammatory M2 phenotype, as well as by suppressing the production of inflammatory cytokines including tumor necrosis factor alpha (TNF- α) and IFNγ [20, 21]. IL-10 plays a complex role in regulating inflammation including activating the JAK/STAT pathway to inhibit the release of pro-inflammatory mediators, mediating the function of T lymphocytes, and furthermore augmenting activation of immune cells including mast cells, NK cells, dendritic cells (DCs), and B cells [22]. IL-6 has both pro-inflammatory and anti-inflammatory effects, with recent attention focused on it's anti-inflammatory properties [23, 24]. IL-6 suppresses the secretion of pro-inflammatory cytokines including interleukin-1 (IL-1), TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN-γ as well as inhibits T-regulatory cells [24].

MSCs directly secrete TGF-β, TSG-6, PGE2, IL-1ra, and IDO and these factors are critical in MSCs' ability to be both anti-inflammatory and immunomodulatory. While PGE2 and TGF-β have anti-inflammatory properties on their own and play a role in regulating T cells and macrophages, they also notably amplify the expression of TSG-6 [25, 26]. TSG-6 has been shown to inhibit inflammatory responses by directly modulating endothelial cells, neutrophils, mast cells, macrophages, vascular smooth muscle cells, and fibroblasts [25]. Furthermore, TSG-6 has been implicated in altering the expression of p38, c-Jun N-terminal kinases (JNK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), thereby suppressing inflammatory cytokine release [19, 25]. PGE2, IDO, and IL-1ra all exerts effects on macrophages, specifically stimulating anti-inflammatory macrophage M2 differentiation [26]. All of these properties together account for their robust anti-inflammatory effect.

Immunomodulatory properties

MSCs have extensive immunomodulatory properties that mediate both the adaptive and the innate immune response. As illustrated above, MSCs secrete various cytokines and factors that inhibit B cells, T cells, NK cells, cytotoxic T cells (CTLs), DCs and B cells, while promoting macrophage polarization to the M2 phenotype [16]. Inhibition of DCs results in lower levels of IL-12, IFN-γ, and TNF-α secretion and moreover impaired antigen presentation [27]. MSCs have the ability to significantly reduce NK cell proliferation, which ultimately inhibits cytotoxic effects as well as alters the production and secretion of IL-6, IL-10, IFN-γ, and TNF-α [27]. The effect of MSCs on B-cells is controversial. Majority of evidence indicates MSCs inhibit B-cells [28, 29]. However, emerging evidence demonstrates MSCs can also stimulate B-cell proliferation and antibody secretion depending on the microenvironment [28]. MSCs have a robust effect on T cells. They express chemokine receptor 3 (CXCR3) and chemokine receptor 5 (CXCR5) which help recruit and stimulate regulatory T cells (Tregs) to prevent inflammation, while inhibiting CD4 + T helper cells and CD8 + CTLs [27, 30–32]. This polarization of T cells towards an immunosuppressive regulatory phenotype is thought to significantly contribute to MSCs ability to reduce inflammation [30].

Anti-bacterial properties

MSCs have demonstrated anti-bacterial properties. As elucidated above, MSCs have significant roles in immunoregulation and inflammation which lend them unique anti-bacterial properties in their ability to modulate T cells, macrophages, and neutrophils while mediating cytokine milieus to combat bacteria [33, 34]. MSCs have been shown to express IDO and interleukin- 17 (IL-17), which aid in bacterial clearance and inhibit bacterial growth [34, 35]. Importantly, MSCs produce and secrete AMPs such as human β-defensin-2, lipocalin-2, LL-37, and hepicidin [34, 36]. Additionally, antimicrobial peptides (AMPs) are crucial for the innate immune response given they directly kill bacteria by disrupting the cellular membrane as well as release pro-inflammatory cytokines which recruit immune cells and further aid in the destruction of bacteria [36]. Ultimately, these properties enable MSCs to impair growth of both gram positive and gram negative bacteria which has critical implications for use in sepsis [33].

Results from human clinical trials utilizing MSCs in sepsis

There have been numerous clinical trials utilizing MSCs in both acute and chronic conditions including myocardial infarction, heart disease, acute respiratory distress syndrome (ARDS), kidney injury with all trials demonstrating safety and trials demonstrating mixed efficacy results [4, 37–39]. To date, there have been 7 completed, 3 active, and 1 unknown status MSC clinical trials for sepsis (Table 1). Two of the trials utilized bone marrow-derived MSCS with the RuMCeSS trial demonstrating an improvement in the SOFA score and 28-day survival of septic patients, and the CISS trial demonstrating an attenuation effect of pro-inflammatory cytokines including IL-1β, interleukin-2, IL-6, IL-8, and monocyte chemoattractant protein 1 [6, 9, 40]. Based off the promising results from the CISS I trial, two larger phase II CISS trials are actively recruiting, of which one utilizes bone marrow-derived MSCs and the other utilizes umbilical cord-derived MSCs [41, 42]. He et al. performed a single injection, dose-escalation trial utilizing umbilical cord-derived MSCs in severe sepsis and found a reduction in IL-6, IL-8, and c-reactive protein (CRP) at day 8 with no dose effect [8]. There were 3 trials utilizing adipose-derived MSCs. The CELLULA trial studied the immune response in healthy subjects with lipopolysaccharide (LPS)-induced sepsis and found that high doses of MSCs (4 million cells/kg) elicited mixed pro-inflammatory and anti-inflammatory effects with increased IL-8, IL-10, TGF-β and nucleosome release, as well as an augmented coagulation activation with a reduced fibrinolytic response [7]. Alp et al. performed 5 serial injections of adipose-derived MSCs and found improved survival rates in the first week of sepsis with a decrease in SOFA scores, CRP, and white blood cells (WBCs). There were no changes in cytokine levels measured [10]. SEPCELL also utilized adipose-derived MSCs for patients with severe bacterial pneumonia (all of which met criteria for sepsis) and found no significant effects of MSCs in this patient population [43]. Lastly, the AMETHYST trial used enhanced MSCs (GEM00220) for bacterial sepsis and published a late-breaking abstract demonstrating safety, however full results evaluating efficacy have not been published [11].

Table 2 highlights the heterogeneity of methods, breaking down completed trials into cell isolation source, number of donors, doubling times in culture, fresh vs. cryopreserved cells used, and viability at time of injection. Umbilical Cord-derived mesenchymal stem (stromal) cells for treatment of severe sepsis, CELLULA, and CISS were the three trials that specified utilizing fresh cells thawed from a master bank, and those three were the only trials to demonstrate changes in inflammatory cytokines [7–9, 40]. The RuMCeSS trial was the only trial to use multiple donors and have the lowest doubling time in culture, with three or less passages [6]. While RuMCeSS was one of two of the reported studies to have a short-term improvement in SOFA score and survival, this methodology did not translate into an apparent long-term survival benefit or modulation of inflammatory cytokines [6]. AMETHYST, SEPCELL, and RuMCeSS used cryopreserved cells, and while AMETHYST and SEPCELL were the only two trials that did not report any signs of efficacy including improvement in SOFA scores or changes in biomarkers, RuMCeSS did have short-term efficacy [6, 11, 43].

Challenges and future perspective

It is well established that MSCs have a wide range of properties that make them a promising therapy for sepsis. However, there are multiple clinical challenges that need to be addressed including ideal cell source, dosage, ideal number of injections, and delivery route prior to MSCs becoming a bench to bedside therapy [4, 13, 44].

The MSC product quality and therefore efficacy relies heavily on isolation, culture expansion, method of cryopreservation, and method of thawing and delivery [44]. Results have demonstrated that long-term culture and expansion of MSCs results in MSC senescence, diminished proliferation, diminished differentiation, and decreased cytokine secretion, thereby limiting the amount of expansion in vitro [44, 45]. As highlighted in Table 2, there is no standard of MSC culture and expansion for clinical trials. Of the 7 MSC sepsis published trials, the doubling times reported are vastly different; the RumCess trial utilized cells that were in culture for 3 or less passages, while on the other spectrum the CELLULA trial utilized cells from 12 to 16 and CISS 12 or fewer. Furthermore, there is a mixture of injecting fresh cells versus cryopreserved. The ability to use cryopreserved cells gives MSCs more widespread applicability. Dave et al. performed a large analysis comparing fresh versus cryopreserved MSCs and found that for most outcomes measured, there was no difference in the in vivo efficacy or in the in vitro potency of MSCs [46]. In order for cells to be truly available in all settings from the emergency department to the ICU, a quick and feasible method of storage, thawing, and delivery of cells needs to be established.

Another major challenge of MSC therapy is determining the optimal cell dose, number of doses, and route of delivery. In the trials discussed here, the cell dosages ranged from 250,000 cells/kg to 300 million (Table 2). Some trials were single dosage, while others employed serial injections. Some cells were delivered intravenously, while others through a central line. Ultimately, there is no clear consensus on dose nor number of injections.

Table 1 Active and completed registered clinical trials using mesenchymal stem cells (MSCs) in sepsis

Clinical Trials using Mesenchymal Stem/Stromal Cells in Sepsis									
Trial Name	**Trial Registration**	**Phase**	**Type of Sepsis**	**MSC Cell Type**	**Dose**	**Patients (*N*)**	**Primary Endpoint**	**Secondary Endpoint**	**Results**
RuMCeSS trial [6]	NCT01849237	I	Septic shock	Allogeneic Bone marrow	1 million/kg	27 total 14 study 13 control	Mortality	Efficacy- organ dysfunction, inflammatory parameters, SOFA score	Improvement in short-term (28-day) survival and SOFA improvement, but did not prevent long-term death
Umbilical cord-derived mesenchymal stem (stromal) cells for treatment of severe sepsis [8]	ChiCTR 14,005,094	I	Severe sepsis	Allogeneic Umbilical cord	Low (1 million cells/kg) Intermediate (2 million cells/kg) High (3 million cells/kg)	30 total 15 study 15 control	Infusion events and serious adverse events	Mortality 28- and 90-; inflammation biomarkers	Safe; possible efficacy in low sample size. Reduced inflammatory biomarkers (L-6, IL-8, TNF-a, CRP)
CELLULA [7]	NCT02328612	I	Healthy subjects induced with LPS to mimic sepsis	Allogeneic Adipose	1st arm- 250,000 cells/kg 2nd arm- 1 million cells/kg 3rd arm- 4 million cells/kg	32 total 24 study 8 control	Safety	Efficacy	High dose (4 million cells/kg) had clear signs of biological activity demonstrating a variety of proinflammatory, anti-inflammatory, and procoagulant effects during endotoxemia
CISS trial [9, 40]	NCT02421484	I	Septic shock	Allogeneic Bone marrow	300,000 cells/kg 1 million cells/kg 3 million cells/kg	30 total 9 study (3 per dose) 21 control	Safety	Plasma cytokine profiling changes	Safe Showed modulation of pro-inflammatory cytokines
Effect of Mesenchymal Stromal Cells on Sepsis and Septic Shock [10]	NCT05283317	I	Study group- UTI, pneumonia, abdominal, meningoencephalitis, bacteremia Control- mostly respiratory	Allogeneic Adipose	1 million cells/kg on the 1st, 3rd, 5th, 7th, and 9th days of therapy	30 total 10 study 20 control	Mortality (28-day survival)	Length of stay in hospital	Positive impact on survival rates of sepsis during the early phases (first week) Decrease in CRP in study group, otherwise no changes in cytokine levels. Decrease in SOFA score.
AMETHYST [11]	NCT04961658	I	Bacterial sepsis	Enhanced MSCS (GEM00220)	15 million 60 million 150 million 150 million x2	11 total	Safety (major morbidity and mortality)	Early signals of benefit	Safe
SEPCELL [43]	NCT03158727	Ib/IIa	Severe community-acquired bacterial pneumonia	Allogeneic Adipose (Cx611)	160 million cells x2 (days 1 and 3)	83 total 42 study 41 placebo	Safety- hypersensitivity reactions, thromboembolic events, and immunological responses	Clinical cure rate, ventilation-free days, and overall survival (Day 90)	Safe and well tolerated No significant effects
ACTIVE TRIALS OR NO RESULTS POSTED YET									
CHOCMSC [50]	NCT02883803	II	Sepsis with organ failure	Allogeneic heterogenous MSCs	1 million/kg	65	Improved SOFA score		No results posted, unknown status

Table 1 (continued)

Clinical Trials using Mesenchymal Stem/Stromal Cells in Sepsis									
Trial Name	**Trial Registration**	**Phase**	**Type of Sepsis**	**MSC Cell Type**	**Dose**	**Patients (*N*)**	**Primary Endpoint**	**Secondary Endpoint**	**Results**
Safety and efficacy of human umbilical cord mesenchymal stem cells for the treatment of sepsis induced by pneumonia [51]	ChiCTR2100050544	I	Pneumonia	Allogeneic Umbilical	1 million/kg	40 total 20 study 20 control	Safety (SAEs or AEs)	Efficacy (improved SOFA, APACHE II)	No results posted, possible ongoing trial
UC-CISSII [42]	NCT05969275	II	Septic Shock	Allogeneic Umbilical	300 million	296	Days free from mechanical ventilation and/or vasopressors and/or renal replacement therapy	Biomarkers, safety, clinical outcome measures, and a health economic analysis	Active trial
CISS2 [41]	NCT03369275	II	Septic Shock	Allogeneic Bone Marrow	300 million	114	Reduction in days on mechanical ventilation, renal replacement, or vasopressors Safety (incidence of treatment-emergency adverse events)	Markers of vascular permeability Mortality (through 12 months) SOFA (through 90 days) Length of ICU stay, hospital stay, hospital readmissions Patient reported outcomes	Active trial

As highlighted above, a major limitation of effectively evaluating MSC therapy efficacy is the heterogeneity of studies (Table 2). Current clinical trials have a small number of patients making it hard to extrapolate data, and analysis is further challenged by the differences in cell sources, dosages, and methods of preparation and delivery. An important discrepancy among trials is determining the best source of MSCs; there are differences in MSCs isolated from adipose versus bone marrow versus umbilical cord. For example, Li et al. found that adipose-derived MSCs are superior in proliferation capabilities and secretion of certain proteins like basic fibroblast growth factor, interferon-γ, and insulin-like growth factor-1, however bone marrow-derived MSCs were superior in osteogenic and chondrogenic differentiation potential and secretion of stem cell-derived factor-1 and hepatocyte growth factor [47]. Kern et al. compared all 3 sources and found differences in success of isolation (with bone marrow having the highest success rate), proliferation ability (umbilical cord-derived being the most proliferative and surviving longest in culture), and differentiation capacity [48]. Another major limitation in interpreting these results is the complexity of sepsis. Sepsis can be caused by urinary tract infection, skin/soft tissue infection, blood infection, lung infection, abdominal infection, meningitis and current clinical trials do not delineate these differences or are underpowered to appropriately evaluate.

Another major limitation in interpreting MSC efficacy is the lack of long-term data. The longest follow-up period reported in the trials discussed here was 90 days. When we expanded the literature search to all MSC trials that included a mix of septic and non-septic patients, we found only one study with long-term follow up. Specifically, Chen et al. found no serious adverse effects 5 years after MSC transplantation in patients with ARDS secondary to Influenza A [49]. Extrapolating from MSC studies not performed in sepsis, in an 81-patient study injecting both allogeneic bone marrow and/or umbilical cord MSCs in patients with Lupus, there were no transplanted related mortality events 5 years post injection and in fact there was a clinical benefit with evidence of

Table 2 Methods for the completed registered clinical trials using mesenchymal stem cells (MSCs) in sepsis. Each trial evaluated for cell derivation, number of donors, amount of doublings in culture, use of fresh versus cryopreserved cells, cell protocol details, and viability at time of injection

Methodology for Completed Registered Clinical Trials using Mesenchymal Stem/Stromal Cells in Sepsis

Trial	Cell Source	# of donors	Doublings	Fresh or Cryopreserved	Cell Protocol Notes	Viability at time of Injection
RuMCeSS[6]	Bone Marrow	Multiple	[50]3 or less (based off prior trial methods)	Cryopreserved in DMSO	[13]Based off prior trial methods: cells cultured in hypoxic conditions	[50]Based off prior trial methods: Cell viability checked during harvesting Cells checked for the "absence of visible clumps or contaminants"
Umbilical cord-derived mesenchymal stem (stromal) cells for treatment of severe sepsis[8]	Umbilical	1	5 or fewer	Fresh (after thawed from master bank)	Cells thawed from master bank and placed in culture for 5-10 days on a weekly basis (discarded if not used during this period)	Criteria: Greater than 90% Actual: 90% to 95% Endotoxin measurement of less than 2 EU
CELLULA[7]	Adipose	1	12-16	Fresh (after thawed from master bank)	Cells thawed and cultured for unspecified length of time prior to injection	"ISCT criteria for MSCs and were thoroughly checked for viability, population doublings, morphology, potency, identity, purity, sterility and genetic stability, among other quality controls"
CISS Trial[9, 40]	Bone Marrow	1	12 or fewer	Fresh (after thawed from master bank)	1. Isolated and cultured to yield 500-800 million MSCs 2. Cryopreserved at 90% viability 3. Thawed and placed back into culture for 5-12 days	Criteria: greater than 80% Actual: 89.4%-96.3%
Effect of Mesenchymal Stromal Cells on Sepsis and Septic Shock[10]	Adipose	1	Not specified	1st 2 injections cryopreserved Next 3 injections fresh (from cryopreserved batch)	For same day injection, cells thawed and suspended in physiological saline solution, then transferred to the patient with a temperature-controlled bag	92.2% ± 2.5
AMETHYST[11]	Enhanced	Not specified	Not specified	Cryopreserved	Not specified	Not specified
SEPCELL[43]	Adipose	Not specified	Not specified	Cryopreserved	[51]Based off prior trial methods: cells expanded through unspecified amount of passages and at various unspecified stages, cells tested for "viability, population doublings, morphology, potency, identity, purity, sterility and genetic stability, among other quality controls"	Not reported

long-term clinical remission [50]. There was one patient who developed bladder cancer four years after MSC transplantation, however the lack of a control group and the use of immunosuppressive drugs such as CYC in this patient make it difficult to interpret whether this was an MSC-related event [50]. In a large meta-analysis evaluating the safety and efficacy of MSCs in acute myocardial infarction, Lee et al. found a trend toward decreased major adverse cardiac events and sustained enhanced left ventricular ejection fraction for up to 36 months post MSC transplantation [51]. In a small 10 patient study evaluating umbilical cord MSC transplantation in multiple sclerosis and neuromyelitis optica, there were no intolerant adverse events including tumor formation or peripheral organ/tissue disorders in a 10-year follow up period [52].

Ultimately, rigorously conducted, multi-center clinical trials with large sample sizes, homogenous cell methods, clearly defined septic populations, and long-term follow up are necessary to demonstrate clear clinical outcomes.

Conclusion

Despite significant advances in early recognition and antibiotic therapies, conventional medications fall short of mitigating the overactive immune and inflammatory response secondary to the sepsis cascade [53]. MSCs hold significant promise for use in sepsis by virtue of their anti-inflammatory, immunomodulatory, and antibacterial properties [27, 53]. All current clinical trials utilizing MSCs in sepsis have clearly demonstrated safety with an array of efficacy results. Future trials will need to focus on rigorous methodology that includes standardization of cell derivation, dosage, and delivery. Addressing these limitations will be crucial for making MSCs a widespread bench to bedside sepsis therapy.

Abbreviations

AMPs	Antimicrobial peptides
ARDS	Acute respiratory distress syndrome
CRP	C-reactive protein
CTL	Cytotoxic T cells
CXCR3	Chemokine receptor 3
CXCR5	Chemokine receptor 5
DCs	Dendritic cells
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferon gamma
IL-10	Interleukin-10
IL-17	Interleukin-17
IL-1	Interleukin-1
IL-1b	Interleukin-1 beta
IL-1ra	Interleukin 1 receptor antagonist
IL-4	Interleukin-4
IL-6	Interleukin-6
JNK	C-Jun N-terminal kinases
LPS	Lipopolysaccharide
MSC	Mesenchymal stem cell
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK cells	Natural killer cells
PGE2	Prostaglandin E2
TGF-β	Transforming growth factor beta
Th	T helper
TLR3	Toll-like receptor 3
TNF-α	Tumor necrosis factor alpha
TNFR	Tumor necrosis factor receptor
TSG-6	Tumor necrosis factor-stimulated gene-6
WBCs	White blood cells

Supplementary Information

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Supplementary Material 1

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The authors declare that they have not use AI-generated work in this manuscript.

Author contributions

CPB: conception, data acquisition, data analysis, manuscript drafting, final approval; JMH: data acquisition, data analysis, manuscript editing, final approval; SYY: data acquisition, data analysis, manuscript editing, final approval; JWW: data acquisition, data analysis, manuscript editing, supervision, final approval.

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Data availability

Cochrane library and clinicaltrials.gov using the keywords "mesenchymal stem cells" and "sepsis" and "clinical trials."

Declarations

Ethics approval and consent to participate

n/a.

Consent for publication

All authors have given consent for publication in Stem Cell Research & Therapy.

Competing interests

JMH is the Chief Scientific Officer, a compensated consultant and advisory board member for Longeveron, and holds equity in Longeveron. JMH is also the co-inventor of intellectual property licensed to Longeveron. The University of Miami also stands to gain royalties from the commercialization of the IP. JMH and CPB have a patent for monitoring efficacy of mesenchymal stem cell therapy. The other authors declare no competing interests.

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