Evolutionary Therapeutic Strategies

Expanded Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) as a Therapeutic Strategy In Managing Critically Ill COVID-19 Patients: The Case for Compassionate Use

Sairam Atluri, MD[1], Laxmaiah Manchikanti, MD[2], and Joshua A. Hirsch, MD[3]

From: [1]Tri-State Spine Care Institute, Cincinnati, OH; [2]Pain Management Centers of America, Paducah, KY; [3]Massachusetts General Hospital and Harvard Medical School, Boston, MA

Dr. Atluri is Medical Director, Tri-State Spine Care Institute, Cincinnati, OH. Dr. Manchikanti is Co-Director, Pain Management Centers of America, Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, and Professor of Anesthesiology-Research, Department of Anesthesiology, School of Medicine, LSU Health Sciences Center, New Orleans, LA. Dr. Hirsch is Vice Chair and Service Line Chief of Neurointerventional Radiology, Chief of Neurointerventional Spine, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Address Correspondence:
Laxmaiah Manchikanti, MD
67 Lakeview Drive
Paducah, Kentucky 42001
E-mail: drlm@thepainmd.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Dr. Hirsch is a consultant for Medtronic and Neiman Health Policy Institute: Grant recipient.

Manuscript received: 03-13-2020
Revised manuscript received: 03-18-2020
Accepted for publication: 03-20-2020

Free full manuscript: www.painphysicianjournal.com

COVID-19 has affected the United States leading to a national emergency with health care and economic impact, propelling the country into a recession with disrupted lifestyles not seen in recent history. COVID-19 is a serious illness leading to multiple deaths in various countries including the United States. Several million Americans satisfy the Center for Disease Control and Prevention (CDC) criteria for being high risk. Unfortunately, the available supply of medical beds and equipment for mechanical ventilation are much less than is projected to be needed. The World Health Organization (WHO) and multiple agencies led by the CDC in the United States have attempted to organize intensive outbreak investigation programs utilizing appropriate preventive measures, evaluation, and treatment.

The clinical spectrum of COVID-19 varies from asymptomatic forms to conditions encompassing multiorgan and systemic manifestations in terms of septic shock, and multiple organ dysfunction (MOD) syndromes. The presently approved treatments are supportive but not curative for the disease. There are multiple treatments being studied. These include vaccines, medications Remdesivir and hydroxychloroquine and potentially combination therapy. Finally, expanded umbilical cord mesenchymal stem cells or (UC-MSCs) may have a role and are being studied.

The cure of COVID-19 is essentially dependent on the patients' own immune system. When the immune system is over activated in an attempt to kill the virus, this can lead to the production of a large number of inflammatory factors, resulting in severe cytokine storm. The cytokine storm may induce organ damage followed by the edema, dysfunction of air exchange, acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection, which may lead to death. Thus, at this point, the avoidance of the cytokine storm may be the key for the treatment of HCOV-19 infected patients.

In China, where there was limited availability of effective modalities to manage COVID-19 several patients were treated with expanded UC-MSCs. Additionally, the Italian College of Anesthesia, Analgesia, Resuscitation and Intensive Care have reported guidelines to treat coronavirus patients with stem cells in the hope of decreasing the number of patients going to the ICU, and, also relatively quickly getting them out of ICU.

In this manuscript, we describe the urgent need for various solutions, pathogenesis of coronavirus and the clinical evidence for treatment of COVID-19 with stem cells. The limited but emerging evidence regarding UC MSC in managing COVID-19 suggests that it might be considered for compassionate use in critically ill patients to reduce morbidity and mortality in the United States.

The administration and Coronavirus Task Force might wish to approach the potential of expanded UC-MSCs as an evolutionary therapeutic strategy in managing COVID-19 illness with a 3-pronged approach: If proven safe and effective on a specific and limited basis…

1. Minimize regulatory burden by all agencies so that critically ill COVID-19 patients will have access regardless of their financial circumstance.

2. Institute appropriate safeguards to avoid negative consequences from unscrupulous actors.
3. With proper informed consent from patients or proxy when necessary, and subject to accumulation of data in that cohort, allow the procedure to be initiated in critically ill patients who are not responding to conventional therapies.

Key words: Coronavirus, COVID-19, cytokine storm, multiorgan failure, expanded umbilical cord mesenchymal stem cells

Pain Physician 2020; 23:E71-E81

1.0 Introduction

COVID-19 was initially concentrated in two regions of China. It has now moved to multiple other countries, including Italy with Europe becoming the new epicenter. The novel coronavirus 2019-nCoV (COVID-19) has reached pandemic proportions across the world after originating in Wuhan (1-9) with a reported mortality of 2.3% (4) and 4.3% in hospitalized patients in China (5). This led to extensive measures being undertaken in the United States with declarations of emergency and interruption of daily lives (10). As of March 18, 2020, the World Health Organization (WHO) has reported almost 220,000 confirmed cases of COVID-19 globally. There have been 9,000 deaths while 85,000 patients have recovered. In the United States (US), the Centers for Disease Control and Prevention (CDC) has counted almost 10,000 COVID-19 cases with over 200 deaths (11). In the US, several million are at high risk including the approximately 1.3 million people are living in nursing homes. Current models regarding COVID 19 estimate hospitalizations of 4.8 million, 1.9 million patients requiring admission to intensive care units (ICUs), and 960,000 would require mechanical ventilation (12,13). However, the United States has approximately 4,900 acute care hospitals, an estimated maximum of 550,000 staffed beds and 95,000 ICU beds with maximum of 200,000 mechanical ventilation units (12). Health care expenditures are expected to skyrocket, along with economic strain on many sectors of the economy (14,15). There have been numerous publications with widespread precautions for prevention, identification, and treatment of these patients (16-45).

On February 11, 2020, the WHO Director General, Dr. Ghebreyesus, announced that the disease by new CoV was a "COVID-19" which is the acronym of "coronavirus disease 2019" (13). In the past 20 years, 2 coronavirus epidemics have occurred with a large-scale epidemic beginning in China and involving over 20 countries leading approximately 8,000 cases and 800 deaths, and the MERS-CoV originating in Saudi Arabia with approximately 2,500 cases and 800 deaths, still causing sporadic cases. The new COVID-19 virus seems to be very contagious and has quickly spread globally.

The clinical spectrum of COVID-19 varies from asymptomatic or pauci-symptomatic forms to clinical conditions characterized by respiratory failure requiring mechanical ventilation and support in the ICU, to multiorgan and systemic manifestations such as sepsis, septic shock, and multiple organ dysfunction (MOD) syndromes (4-7,13). In one of the first reports on the disease, Huang et al (17) showed about one-third of the patients with pneumonia (13, 32%) required ICU care, and there were 6 (15%) fatal cases. In the United States, Arentz et al (8) published characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State with descriptions of clinical presentation, characteristics, and outcomes of incident cases of COVID-19 admitted to the intensive care unit. Among 21 cases, comorbidities were identified in 18 cases (86%), with chronic kidney disease and congestive heart failure being the most common. Initial symptoms included shortness of breath (76%), fever (52%), and cough (48%), with mean onset of symptoms prior to presenting to the hospital of 3.5 days, and 17 patients (81%) were admitted to the ICU less than 24 hours after hospital admission. Acute respiratory distress syndrome (ARDS) was observed in 15 of 15 patients requiring mechanical ventilation and 8 of 15 (53%) developed severe ARDS by 72 hours. As of March 17, 2020, mortality was 67% and 24% of patients have remained critically illness and only 9.5% have been discharged from the ICU. This case series provided additional data for United States population with high rate of cardiomyopathy, the causation of which may be either overwhelming critical illness or a direct cardiac complication, being investigated to better characterize this risk.

As the medical profession has recognized quickly,

there is no cure presently for this disease and vaccination would not be available for several months. This leaves a large unmet need for a safe and effective treatment for COVID-19 infected patients, especially the severe cases (12,13,16,17).

Multiple treatment strategies in the pipeline include antiviral therapy (1,16,36,37), hydroxychloroquine and combinations (34,35,37,39), neutralizing antibodies (18-21), repurposing currently available antiviral medications (1,16,22-28,36,37), and passive antibody transfer from convalescent patients' sera (29,30). Other new therapies include development of blocking agents that bind to ACE2 receptor (31-33,46-49). ACE2-positive cells are infected by the HCoV-19, like SARS-2003 (50,51). The ACE2 receptor is widely distributed on human cell surface, especially the alveolar type II cells (AT2) and capillary endothelium (52), and the AT2 cells highly express TMPRSS2 (53).

While immunological therapy may be feasible, the immunomodulatory capacity may be not strong enough, if only one or 2 immune factors were used, as the virus can stimulate a cytokine storm in the lung. Cytokine storm can lead to acute respiratory distress syndrome (ARDS), acute cardiac injury, secondary infection, leading to generalized sepsis and multisystem failure, which may lead to death (3,17). Thus, avoiding the cytokine storm may be the key for the treatment of COVID-19 infected patients.

Since there are a lack of effective therapies and immunological treatments may be insufficient, mesenchymal stem cells (MSCs), owing to their powerful immunomodulatory ability, may have beneficial effects for preventing or attenuating the cytokine storm and reducing morbidity and mortality of this disease.

Cell-based therapies are being incorporated into treatment plans for a number of disease processes including pulmonary (54-60), cardiovascular (61-63), hepatic (64-66), renal (67-69), and other conditions (60,70-76). Generally, the use of cell-based therapy has greatly outpaced the evidence (60,70-76). Unfortunately, this led to unsubstantiated claims of miraculous outcomes (77). As a result, the Federal Trade Commission (FTC) has taken action against stem cell therapy clinics found to be in violation of the truth in advertising law (78). Subsequently, the Food and Drug Administration (FDA) has investigated multiple stem cell clinics and published new guidance (79-94). Further, the sheer volume of unsubstantiated claims and lack of high level research has led to a Health Canada policy position paper on the use of autologous cell therapy products (95). Despite and in full view of the above, stem cell therapy may have a role in managing COVID-19 disease (3,16,59,96-101). The news of reports of stem cell therapy in China with publication of the details of a case of a critically ill 65-year old Chinese woman infected with COVID-19, whose conditions improved after the infusion of MSCs (96,97). They also reported that 7 other coronavirus patients in Beijing who had the stem cell therapy responded in a similar way (3).

The newspaper also noted that this case is one of many using stem cells to treat coronavirus patients in China, according to the WHO's clinical trial database. Zhang Xinmin, director of biological technology at the Ministry of Science and Technology in Beijing, told a press conference on February 15 that the preliminary results of stem cell experiments conducted across the country suggested the technology was "safe and effective". Such statements should be interpreted with caution (45).

2.0 Pathogenesis of Coronavirus

The S protein on Coronavirus surface specifically recognizes the spike protein in the angiotensin I converting enzyme 2 receptor (ACE2) of the exposed cell and after binding, the virus enters the cell thereby infecting it (1,3,47-53). Unfortunately, the ACE2 receptor is widely distributed on the human cells surface, especially the AT2 of the lungs (52,57). ACE2 receptors are also abundantly found in the heart, liver, digestive organs and kidneys. In fact, almost all endothelial cells and smooth muscle cells in organs express ACE2, therefore once the virus enters the blood circulation, it spreads widely. All tissues and organs expressing ACE2 could be the battlefield of the novel coronavirus and immune cells. This explains why beyond ARDS, patients might also experience acute myocardial injury, arrhythmia, acute kidney injury, shock, and death from MOD syndrome (3,17). However, the cure of COVID-19 is essentially dependent on the patient's own immune system. When the over activated immune system kills the virus, it produces a large number of inflammatory factors, resulting in severe cytokine storm (3,17). The main reason for organ damage may be due to virus-induced cytokine storm caused by IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα, followed by the edema, dysfunction of the air exchange, ARDS, acute cardiac injury and the secondary infection, which may lead to death (17).

3.0 Treatment of COVID-19

Pharmaceuticals and research labs across the world are racing to find vaccines and treatments for the new coronavirus, using a variety of different technologies (42). According to Benjamin Neuman, a virologist, "immunizing against the pathogen is not only a longshot, but there has never been a very successful human vaccine against any member of the coronavirus family" (42).

President Trump urged scientists to speed up the process of development of vaccine and treatment, but experts do not express optimism due to fundamental constraints, which leave little wiggle room (42). A vaccine must have a fundamental scientific basis, be safe and manufacturable, which could take a year and a half or even longer (42). However, thankfully, initial reports are encouraging with potential development of vaccine much sooner.

The next drug is Remdesivir, which could be the closest to market launch (1,16,26,36,37). Other drugs include chloroquine and hydroxychloroquine. Both chloroquine and hydroxychloroquine have been described to be effective (34,35,37,39) however, hydroxychloroquine was shown to be superior to chloroquine with a 5-day treatment. Outside of supportive therapies, of all the treatment modalities linked to COVID-19, expanded umbilical cord mesenchymal stem cells (UC-MSCs) may be the closest to being utilized (3,96-104).

The Italian College of Anesthesia, Analgesia, Resuscitation and Intensive Care have reported guidelines to treat coronavirus patients, which included a statement that stem cells have a serious potential to avoid COVID-19 by decreasing the number of patients going to the ICU and relatively quickly getting them out of ICU (57).

4.0 Role of Stem Cells

At a cellular level, MSCs would appear to have some natural immunity to the coronavirus owing to their powerful immunomodulatory ability. They may also have beneficial effects for preventing or attenuating the cytokine storm by secreting powerful anti-inflammatory factors. MSC therapy can theoretically inhibit the overactivation of the immune system and promote endogenous repair by improving the microenvironment. After entering the human body through intravenous infusion, part of the MSCs accumulate in the lung, which could potentially improve the pulmonary microenvironment, protect alveolar epithelial cells, prevent pulmonary fibrosis and improve lung function (3,54-56,58).

MSCs have been widely used in cell-based therapy, from basic research to clinical trials. Safety and effectiveness have been clearly documented in many clinical trials, especially in the immune-mediated inflammatory diseases, such as graft versus-host disease (GVHD) and systemic lupus erythematosus (SLE) (54-56,58-76) though obviously, they haven't been studied other than very preliminarily in COVID-19. MSCs play a positive role mainly in two ways, namely immunomodulatory effects and differentiation abilities. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells including T cells, B cells, dendritic cells, macrophages and natural killer cells leading to immunomodulation). As indicated in Fig. 1., stem cells are thought to regulate the inflammatory response and promote tissue repair and regeneration.

MSCs also have been shown to improve function in cardiovascular, renal, hepatic, and multiple other disorders (54-56,58-76). This study aims to investigate whether MSC transplantation improves the outcome of 7 enrolled patients with COVID-19 pneumonia.

4.1 Stem Cells are Also Anti-Microbial

One of the concerns based on preclinical science is that the virus can infect the stem cells rendering them ineffective. A study (3) of seven patients with COVID-19 pneumonia (and three controls) in Beijing suggested that the coronavirus was not able infect the injected umbilical cord stem cells. Current data (103-110) suggest that MSCs exert their antimicrobial effects through indirect and direct mechanisms. Indirectly, they influence the role of host immune response against pathogens, especially in the dynamic coordination of the pro- and anti-inflammatory elements of the immune system or by increasing the activity of phagocytes; and directly, by the secretion of antimicrobial peptides and proteins (AMPs), and by the expression of molecules such as indoleamine 2,3-dioxygenase (IDO) and interleukin (IL)-17. MSCs have been reportedly responsible of the bacterial clearance in preclinical models of sepsis, ARDS, and cystic fibrosis infection (109,110). So far, MSCs have been found to constitutively express four AMPs: cathelicidin LL-37, human α-defensin-2 (hBD-2), hepcidin, and lipocalin-2 (Lcn2), which can be further modulated during infection and inflammation. In different preclinical models, MSCs-derived AMPs have demonstrated to be part of the bacterial clearance effect observed with MSCs treatment, suggesting that MSCs can directly enhance the innate immune response to bacterial infection (103). AMPs-mediated cell killing

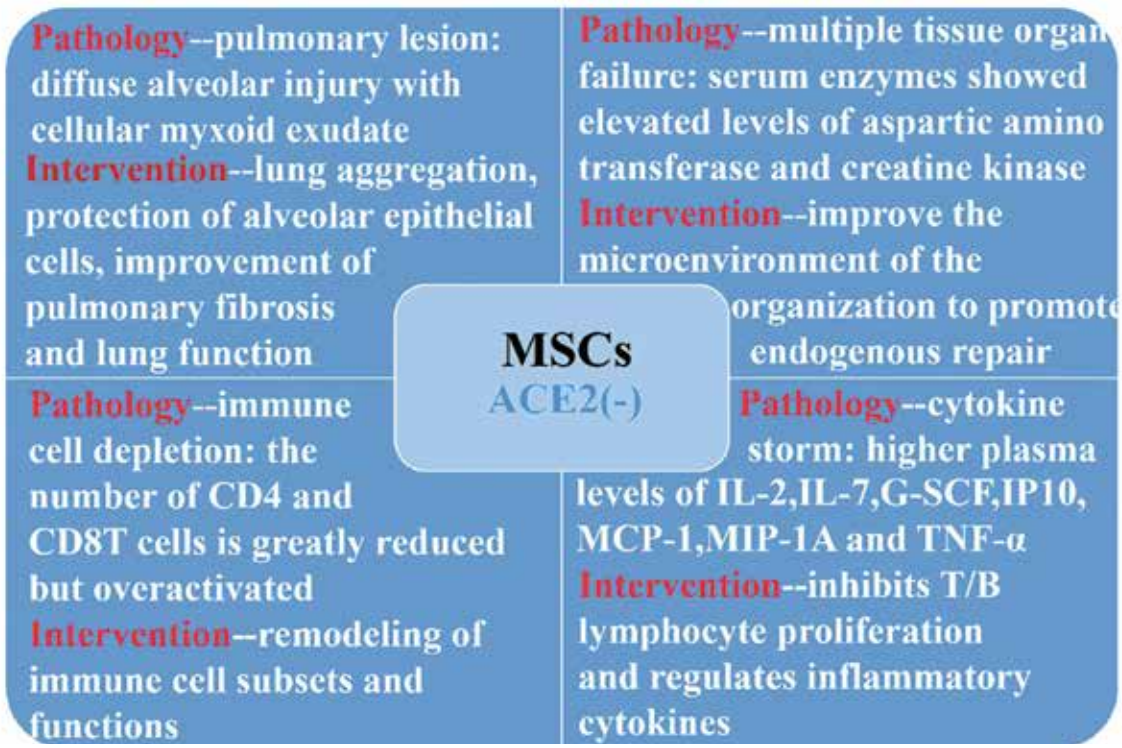

Fig. 1. *ACE2 MSCs benefit the COVID-19 patients via immunoregulatory function*.
Source: Leng Z, Zhu R, Hou W. Transplantation of ACE2 Mesenchymal stem cells improves the outcomes of patients with COVID-19 pneumonia. Aging Dis 2020; 11:216-228 (3).

occurs by disrupting membrane integrity, by inhibiting protein, DNA or RNA synthesis, and by interacting with certain intracellular targets.

5.0 Clinical Evidence of Expanded Mesenchymal Stem Cells

Multiple clinical trials (99-102) using stem cell therapy to treat the Coronavirus from China have been registered at www.clinicaltrials.gov. The published studies include small numbers of patients (3), a case reports (97), and newspaper reports (96,98). The descriptions provided below are from the investigators and/or sponsors of the studies or submitted proposals and reflect their perspectives and understanding of the facts. The studies include a case report (97), one published preliminary report with 7 patients in the treatment group and 3 in the control group with a 14-day follow-up (3), other studies registered to be performed, with information being obtained from submitted protocols.

The first coronavirus case treated with umbilical cord cells was reported from China (97) leading to further to speculation and further investigations. A 65 y/o with severe pneumonia, respiratory failure and multi-organ failure requiring mechanical ventilation was treated with 3 doses each of 50 million allogeneic umbilical cord stem cells, three days apart. This was done in conjunction with conventional therapy to which she was not responding. One day after the second dose, her vital signs stabilized along with the signs of organ failure and she was no longer dependent on the ventilator. 2 days after the third infusion, she was transferred out of the ICU to the regular ward as she recovered with most of her laboratory indexes returning to normal. 6 days after the third infusion, her CT scan changes in the lungs significantly improved. 2 days after the third infusion, her throat swabs were negative for Coronavirus.

In a recently published tiny clinical trial (3), the investigators compared 7 patients (1 critically serious, 4 serious and 2 common) infected with the coronavirus who received one dose of stem cell therapy with 3 patients in the control group (3 serious) who did not.

All these patients were not responding to standard treatment. They were followed for 14 days. All the 7 patients with stem cell therapy recovered. However, in the control group, one patient died while another patient developed ARDS. Only one patient in the control group was stable. No complications were noted in the treatment group. In the treated group within a few days, the oxygen saturation, biomarkers for inflammation and tissue injury like CRP, aspartic aminotransferase, creatine kinase activity and myoglobin normalized. Significant improvements were seen in the radiological signs in the follow up CT scans of the lungs (3). Limitations of this study include the small sample size and short-term follow-up.

The first trial (99) was registered on 2/5/2020 by Beijing 302 Hospital. This phase 1 clinical trial is done to inspect the safety of UC-MSCs therapy for pneumonia patients infected with 2019-nCoV. This multi-center trial is expected to recruit 20 patients. 10 patients will receive 3 IV transfusions of stem cells in the treated group, along with the conventional treatment. In addition, 10 patients receiving conventional treatment will be used as controls. The clinical symptoms, pulmonary imaging, side effects, 28-days mortality, immunological characteristics (immune cells, inflammatory factors, etc.) will be evaluated during the 180 days follow up. The authors (99) opined that, "The features of MSCs, including their regenerative properties and ability to differentiate into diverse cell lineages, have generated interest among researchers whose work has offered intriguing perspectives on cell-based therapies for various diseases." Authors (99) also felt that these findings seem to suggest the potential beneficial effect of MSC-based treatment could be principally due by the immunomodulation and regenerative potential of these cells.

The second trial (100) was registered on 2/13/2020 by Zhongnan Hospital. Per the investigators, this phase 2 trial is being conducted to assess the role of umbilical cord stem cells in treating the 2019-nCOV infection pneumonia.

The third trial (101) was registered on 2/18/2020 by Wuhan Union Hospital. The researchers posit that a large amount of evidence shows that MSCs can migrate to damaged tissues, exert strong anti-inflammatory and immune regulatory functions, promote the regeneration and repair of damaged tissues, resist apoptosis and inhibit tissue fibrosis, and reduce tissue damage (101). They cite studies that have shown that the anti-inflammatory effects of MSCs can significantly reduce virus-induced lung injury and mortality in mice. The purpose of this study is to investigate effectiveness and safety of UC-MSCs in treating severe pneumonia patients infected with 2019-nCoV. This trial is expected to recruit 48 patients, with 24 patients receiving 4 IV transfusion of 5.0 x106 cells/kg of UC-MSCs in the treatment group. All of them also will receive conventional treatment. In addition, another 24 patients receiving conventional treatment will serve as a control group. Based on the study protocol, "The respiratory function, pulmonary inflammation, clinical symptoms, pulmonary imaging, side effects, 28-days mortality, immunological characteristics (immune cells, inflammatory factors, etc.) will be evaluated during the 90 days to 96 weeks follow up (101)."

The fourth trial (102) was registered on 3/3/2020 by the Puren Hospital Affiliated to Wuhan University of Science and Technology. Per the investigators, this clinical trial will be performed to explore the safety and efficacy of UC-MSCs therapy for coronavirus pneumonia patients (102). The investigators planned to recruit 48 patients aged from 18 to 75 years old and had no severe underlying diseases. In the cell treatment group, 24 patients will receive 0.5 x 106 UC-MSCs /kg body weight intravenous treatment 4 times every other day besides conventional treatment. In the control group, other 24 patients will receive conventional treatment plus 4 times of placebo intravenously. The lung CT, blood biochemical examination, lymphocyte subsets, inflammatory factors, 28-days mortality, etc will be evaluated within 24h and 1, 2, 4, 8 weeks after UC-MSCs treatment.

5.1 What Are The Best Stem Cells To Treat Coronavirus?

Largely due to the FDA regulations, currently in the US, stem cell therapy is dominated by autologous bone marrow stem cells (76). MSCs are most commonly used to treat pain resulting from musculoskeletal conditions. Various clinical trials have shown that they are safe and efficacious in this context (74-76,111). Despite the fact that there are few stem cells in the bone marrow they are sufficient to treat spine and joint pain as the injections are very localized. However, they would not likely be ideal to treat coronavirus which is a serious systemic illness.

The other stem cells available for clinical use are adipose stem cells, amniotic stem cells and Umbilical cord stem cells. Amongst these, umbilical cord stem cells seem to be the most desirable for the following reasons.

1. Umbilical cord (especially Wharton jelly) unlike bone marrow has a high concentration of stem cells. It is one of the richest sources of MSC (112).
2. Umbilical cord is an extensive source of stem cells. (113).
3. UC-MSCs have fast doubling times, they can be efficiently expanded in the lab. Since coronavirus is a systemic condition, millions of stem cells need to be injected for clinical efficacy (113). This is easily possible with umbilical stem cells.
4. Additionally, they are scalable which will be important given the large number of expected coronavirus patients (113).
5. UC-MSCs can be extracted noninvasively No procedure is necessary unlike bone marrow or adipose stem cells.
6. Unlike embryonic stem cells (ESCs), it is an afterbirth tissue and is considered medical waste.
7. Unlike bone marrow and adipose stem cells, UC-MSCs show a gene expression profile more similar to that of ESCs which means they have faster doubling times, more plasticity and possibly more potency. Fortunately, unlike ESCs, they are not tumorigenic (114).
8. Although these cells are allogeneic, they seem to be immunoevasive (115) as they express low levels of major histocompatibility complex (MHC) class I molecules, but not MHC class II on their cell surface, allowing their transplantation across MHC barriers.

To summarize, amongst all stem cells, umbilical cord cells seem to be best positioned to treat coronavirus. These are the cells that have been used to treat coronavirus in China.

5.2 What is the Best Route of Administration?

Intravenous infusion seems to be the most desirable route of administration. All the positive reports from China have used this route. It is also the least invasive compared to intra-arterial or tissue injection. Lungs seem to be the most commonly affected organ with the coronavirus. Fortunately, most of the stem cells injected IV, get trapped in the lung. Intuitively, this should likely be beneficial. Additionally, distant injured organs also have positive effects as seen in the study (3) described above. This is possibly from the paracrine effects or by the production of specific exosomes by the stem cells which travel to remote affected organs and perform healing by secreting the necessary immunomodulatory proteins.

5.3 How to Assure Safety of this Treatment?

Quality preparation of the stem cells is of paramount importance. The source of stem cells should be from legitimate labs which are compliant with the FDA standards. There should be zero tolerance for negligence in these labs. Donors should be strictly screened. There should be no room for contamination right from the procurement of the cord tissue to the production of the final product. This product must be analyzed for cell viability, quality of the stem cells and sterility and must meet the highest standards.

During IV infusion, all precautions should be taken to prevent pulmonary or other organ embolization. Patients should be monitored for allergic reactions as we are using an allogeneic product. Numerous complications (45,116) have been reported from improper application of stem cells.

The appropriate cell dose, cell concentration, cell infusion rate should to be determined to maximize efficacy and safety. Cell passage numbers should be limited to increase potency and decrease cell size.

6.0 Evaluation of Coronavirus (COVID-19)

Multiple manuscripts have described evaluation and treatment of COVID-19. In the United States, criteria have been developed for persons under investigation (PUI) for COVID-19. Per the CDC, most patients with confirmed COVID-19 have developed a fever and/or symptoms of acute respiratory illness (i.e., cough, difficulty breathing). Arentz et al (8) reported characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. These critically ill patients initially reported shortness of breath (76%), fever (52%), and cough (48%). The mean onset of symptoms prior to presenting to the hospital was 3.5 days with 17 patients or 81% were admitted to the ICU less than 24 hours after hospital admission. Thus, symptoms reported in the United States are similar to symptoms in China and other countries, some specific concerns with cardiomyopathy were reported in the United States. If a person is a PUI, it is recommended that practitioners immediately put in place infection control and prevention measures. The major concern of COVID-19 infection is that MOD syndromes leading to death (13). Li et al (6) published the case studies, which encapsulated the first 425 cases recorded in Wuhan, China in the New England Journal of Medicine. Patients' ages ranged from 15 to 89 years with a me-

dian age of 59. Both genders were involved equally. Children were not involved. In addition, clinical and epidemiological data from the Chinese CDC and regarding 72,314 case records encompassing confirmed, suspected, diagnosed, and asymptomatic cases were published in the journal of the American Medical Association, providing an important illustration of the epidemiologic curve of the Chinese outbreak (4). The overall case-fatality rate on confirmed cases was 2.3%. Importantly, the fatal cases were primarily elderly patients, in particular those aged above 80 years (15%) and 70 to 79 years (8%). Approximately half of the critical patients and affected by preexisting comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases died. While 1% of patients were aged 9 years or younger, no fatal cases occurred in this group. Wang et al (5) published in JAMA the clinical characteristics of 138 hospitalized patients with COVID-19. In this single center case series, 26% of patients required admission to the ICU and 4.3% died. They presumed that human to human hospital-associated transmission of COVID-19 was suspected in 41% of the patients. In the United States, showing the first description of critically ill patients infected with SARS-COV-2, showed a high rate of ARDS and a high risk of death (8). Overall, as of March 17, 2020, mortality in this group of 21 patients was 67% and 24% of patients have remained critically ill and only 9.5% have been discharged from the ICU. Data from other countries is also similar (117-123).

The clinical manifestations were divided as follows by the Chinese CDC report:

1. Mild disease: non-pneumonia and mild pneumonia occurring in 81% of the cases.
2. Severe disease: this occurred in 14% of the cases
    - Dyspnea
    - Respiratory distress
    - Respiratory rate ≥ 30 per minute
    - Oxygen saturation ≤ 93% at rest state
    - Arterial partial pressure of oxygen (PaO2)/fraction of inspiration O2 (FiO2) ≤ 300 mnHg, 1 mmHg=0.133 kPa
3. Critical disease: this occurred in 5% of the cases with need for ICU
    - Respiratory failure needing mechanical ventilation
    - Septic shock
    - Multiple organ dysfunction (MOD) or failure (MOF)
    - Patients needing ICU

Based on the recommendations of the WHO, collection of the specimens from both the upper respiratory tract, nasal and oropharyngeal samples, and lower respiratory tracts such as expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage is recommended.

7.0 Discussion

The United States is at a crossroads of national emergency with healthcare and economic impact propelling the country into a recession with disrupted lifestyles never seen before in recent history. President Trump has directed scientists and drug companies to speed up the process of prevention and treatment (42,123,124). The guidelines of the Italian College of Anesthesia, Analgesia, Resuscitation and Intensive Care to treat coronavirus patients (57) outlined that:

1. Doctors should make "moral" choices and provide intensive care based on "distributive justice" and the "appropriate allocation" of limited health resources, as seen during wartime catastrophe medicine.
2. The allocation criteria need to guarantee that those patients with the highest chance of therapeutic success will retain access to intensive care.
3. What might be a relatively short treatment course in healthier people could be longer and more resource-consuming in the case of older or more fragile patients.
4. Stem cells have a potential to avoid this by decreasing the number of patients going to the ICU and also relatively quickly getting them out of ICU.

In the United States, President Trump has outlined the required precautions (124). Multiple organizations in the United States spearheaded by the CDC and the FDA have published guidelines.

Based on the present evidence, expanded UC-MSCs shows some promise as a therapeutic strategy in managing COVID-19 illnesses. Others are in development and have been proposed to be utilized based on the same philosophy as expanded umbilical cord stem cells such as exosomes (41-43,104). Antiviral drug therapy with Remdesivir and treatment with hydroxychloroquine are also options for mild disease (1,16,34-36,39,42). However, for severe disease, expanded UC-MSCs may be the readily available option. However, at the present time, the evidence is limited.

Intravenous infusion of expanded allogeneic umbilical cord stem cells seem to be safe and possibly ef-

ficacious based on the early and preliminary reports from China. To achieve the goals of near term compassionate use treatment of critically ill COVID-19 patients, we urge administrators and regulators to consider this 3-pronged approach, if proven safe and effective on a specific and limited basis:

1. US regulatory agencies should minimize the regulatory burden so that properly informed, critically ill COVID-19 patients/proxies will have access to expanded UC-MSC therapy (3,96-98).
2. Safeguards must be instituted so that patients do not suffer any negative consequences from this treatment from unscrupulous actors.
3. Ideally, any patients/proxies consenting for this compassionate use care will be followed and entered into a central data base.

8.0 Conclusion

COVID-19 presents a serious and urgent healthcare crisis. The spectrum includes critically ill patients some of who are nonresponsive to conventional therapies and unlikely to recover. Preclinical and preliminary clinical data suggests that by UCS-MCS through its anti-inflammatory and immunomodulatory actions, can heal tissues thereby enhancing recovery. Additionally, this treatment seems also to be antimicrobial. Easily available allogeneic, expanded, umbilical cord stem cells infused intravenously seems to be a viable alternative. Since the majority of cells get trapped in the lung, this would also seem beneficial as the lung is the primary organ affected by coronavirus. This therapy is relatively inexpensive and noninvasive. In these trying and dangerous times MSC-UC present a potential option for treating critically ill patients under compassionate use protocols.

Acknowledgments

The authors wish to thank Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We would like to thank Alan Kaye, MD, PhD, Editor-in-Chief of Pain Physician, for rapid review and approval for publication.

Author Contributions

The concept of stem cells for COVID-19 was conceived by SA. After further discussions with LM, the concept for the manuscript was developed. The manuscript was completed by all authors.

References

1. Kruse RL. Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China. *F1000Res* 2020; 9:72.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382:727-733.
3. Leng Z, Zhu R, Hou W. Transplantation of ACE2 Mesenchymal stem cells improves the outcomes of patients with COVID-19 pneumonia. *Aging Dis* 2020; 11:216-228.
4. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020 Feb 24. [Epub ahead of print]
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020 [Epub ahead of print].
6. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; Jan 29. [Epub ahead of print]
7. del Rio C, Malani PN. 2019 novel coronavirus –important information for clinicians. *JAMA* 2020 [Epub ahead of print].
8. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020 Mar 19. [Epub ahead of print]
9. World Health Organization (WHO). Confirmed coronavirus cases worldwide tops 125,000 in 118 countries – 4,613 deaths. *SciTechDaily*, March 12, 2020. https://scitechdaily.com/confirmed-coronavirus-cases-worldwide-tops-125000-in-118-countries-4613-deaths/
10. Donald J. Trump, President of the United States. Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak. March 13, 2020. www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/
11. Centers for Disease Control and Prevention. Coronavirus (COVID-19). www.cdc.gov/coronavirus/2019-ncov/index.html Accessed 3/19/2020
12. Holly R. Over-Capacity Challenges Loom Large as US COVID-19 Hospitalizations Projected to Reach 4.8M. Home Health Care News, March 12, 2020. https://homehealthcarenews.com/2020/03/over-capacity-challenges-loom-large-as-us-covid-19-hospitalizations-projected-to-reach-4-8m/
13. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19), If you are at High Risk. www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-risk-complications.html
14. U.S. Burden of Disease Collaborators. The state of US health, 1990–2010:

Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.

15. Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996-2016. *JAMA* 2020; 323:863-884.
16. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). *StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing;* 2020 Jan-.2020 Mar 8.
17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497-506.
18. Tortorici MA, Veesler D. Structural insights into coronavirus entry. *Adv Virus Res* 2019; 105:93-116.
19. Casadevall A, Pirofski LA. The Ebola epidemic crystallizes the potential of passive antibody therapy for infectious diseases. *PLoS Pathog* 2015; 11:e1004717.
20. Shin YW, Chang KH, Hong GW, et al. Selection of vaccinia virus-neutralizing antibody from a phage-display human-antibody library. *J Microbiol Biotechnol* 2019; 29:651-657.
21. Keck ZY, Wang Y, Lau P, et al. Isolation of HCV neutralizing antibodies by yeast display. *Methods Mol Biol* 2019; 1911:395-419.
22. Tsai CH, Lee PY, Stollar V, et al. Antiviral therapy targeting viral polymerase. *Curr Pharm Des* 2006; 12:1339-1355.
23. Anderson J, Schiffer C, Lee SK, et al. Viral protease inhibitors. *Handb Exp Pharmacol* 2009; 189:85-110.
24. Litterman N, Lipinski C, Ekins S. Small molecules with antiviral activity against the Ebola virus [version 1; peer review: 2 approved]. *F1000Res* 2015; 4:38.
25. Dodd LE, Follmann D, Proschan M, et al. A meta-analysis of clinical studies conducted during the West Africa Ebola virus disease outbreak confirms the need for randomized control groups. *Sci Transl Med* 2019; 11:520.
26. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; 11: 222.
27. Li CC, Wang XJ, Wang HR: Repurposing host-based therapeutics to control coronavirus and influenza virus. *Drug Discov Today* 2019; 24:726-736.
28. Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother* 2014; 58:4885-4893.
29. Mire CE, Geisbert JB, Agans KN, et al. Passive Immunotherapy: Assessment of convalescent serum against Ebola Virus Makona Infection in nonhuman primates. *J Infect Dis* 2016; 214: S367-S374.
30. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus* 2016; 14:152-157.
31. Karakus U, Pohl MO, Stertz S. Breaking the convention: Sialoglycan variants, co-receptors and alternative receptors for influenza a virus entry. *J Virol* 2019; 94:4.
32. Wong SK, Li W, Moore MJ, et al. A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *J Biol Chem* 2004; 279:3197-3201.
33. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; 426:450-454.
34. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treat ment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020 Mar 9. [Epub ahead of print]
35. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; 43:185-188.
36. Li H, Wang YM, Xu JY, Cao B. Potential antiviral therapeutics for 2019 Novel Coronavirus. *Zhonghua Jie He He Hu Xi Za Zhi* 2020; 43:170-172.
37. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30:269-271.
38. Vincent MJ, Bergerson E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* 2005; 2:69.
39. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14:72-73.
40. Centers for Disease Control and Prevention. Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19).
www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html
41. Celltex Plans to Launch Program to Use Mesenchymal Stem Cells for COVID-19-related Symptoms Under an Existing Regulatory Study. *Business Wire*, March 16, 2020. Accessed date 3/18/2020.
www.businesswire.com/news/home/20200316005852/en/Celltex-Plans-Launch-Program-Mesenchymal-Stem-Cells.
42. MedicalXpress Breaking News and Events. Coronavirus drugs: Who's doing what, and when they might come. March 17, 2020. Accessed date 3/18/2020.
www.mdlinx.com/pain-management/top-medical-news/article/index.cfm/?publish_dt=03-17-2020&rowNum=7621393&_rw=true&utm_source=alert&utm_medium=email&utm_campaign=ajm_49664&
43. Kimera Exosomes. (MSC) Exosome Laboratory. Accessed date 3/19/2020.
www.kimeralabs.com/
44. Centers for Disease Control and Prevention. Interim Guidance for Healthcare Facilities: Preparing for Community Transmission of COVID-19 in the United States.
www.cdc.gov/coronavirus/2019-ncov/healthcare-facilities/guidance-hcf.html Accessed date 3/18/2020.
45. Knoepfler P. 'We Cannot Stick to the Rules': claims of stem cells saving COVID-19 patients. *The Niche*, March 3, 2020.
https://ipscell.com/2020/03/we-cannot-stick-to-the-rules-claims-of-stem-cells-saving-covid-19-patients/
46. Centers for Disease Control and Prevention. Coronavirus Pandemic Update 37: The ACE-2 Receptor - The Doorway to COVID-19 (ACE Inhibitors & ARBs). Accessed date 3/18/2020.
www.youtube.com/watch?v=1vZDVbqRhyM&feature=youtu.be&fbclid=IwAR3XZZZZmzSk7ltqNuZ5mM19MxRkiv6fhfsNB1LjAR1qte7wmeUXs-vI45U
47. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020;

63:457-460.

48. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; 395:565-574.
49. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579:270-273.
50. Kuba K, Imai Y, Rao SA, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; 11:875-879.
51. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* 2013; 503:535-538.
52. Hamming I, Timens W, Bulthuis ML, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203:631-637.
53. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. *J Virol* 2019; 5:6.
54. Behnke J, Kremer S, Shahzad T, et al. MSC-based therapies-new perspectives for the injured lung. *J Clin Med* 2020; 3:9.
55. Cruz FF, Rocco PRM. The potential of mesenchymal stem cell therapy for chronic lung disease. *Expert Rev Respir Med* 2020; 14:31-39.
56. Li D, Liu Q, Qi L, Dai X, Liu H, Wang Y. Low levels of TGF-β1 enhance human umbilical cord-derived mesenchymal stem cell fibronectin production and extend survival time in a rat model of lipopolysaccharide-induced acute lung injury. *Mol Med Rep* 2016; 14:1681-1692.
57. SIAARTI. Pro Vita Contra Dolorem Semper. Raccomandazioni di etica clinica per l'ammissione a trattamenti intensivi e per la loro sospensione, in condizioni eccezionali di squilibrio tra necessità e risorse disponibili - versione 01 Pubblicato il 06.03.2020.
58. Iyer SS, Co C, Rojas M. Mesenchymal stem cells and inflammatory lung diseases. *Panminerva Med* 2009; 51:5-16.
59. Abraham A, Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. *Stem Cells Transl Med* 2020; 9:28-38.
60. Khatri M, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. *Stem Cell Res Ther* 2018; 9:17.
61. Chen F, Liang P, Ye F, Hou CC, Pi L. Mesenchymal stem cell therapy for patients with ischemic heart failure -past, present, and future. *Curr Stem Cell Res Ther* 2020 Mar 9. [Epub ahead of print]
62. Bartolucci J, Verdugo FJ, González PL, et al. Safety and efficacy of the intravenous infusion of umbilical cord mesenchymal stem cells in patients with heart failure: A Phase 1/2 randomized controlled trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy]). *Circ Res* 2017; 121:1192-1204.
63. Shafei AE, Ali MA, Ghanem HG, et al. Mesenchymal stem cell therapy: A promising cell-based therapy for treatment of myocardial infarction. *J Gene Med* 2017; 19:12.
64. Driscoll J, Patel T. The mesenchymal stem cell secretome as an acellular regenerative therapy for liver disease. *J Gastroenterol* 2019; 54:763-773.
65. Hu C, Zhao L, Wu Z, Li L. Transplantation of mesenchymal stem cells and their derivatives effectively promotes liver regeneration to attenuate acetaminophen-induced liver injury. *Stem Cell Res Ther* 2020; 11:88.
66. Heydari Z, Najimi M, Mirzaei H, et al. Tissue engineering in liver regenerative medicine: insights into novel translational technologies. *Cells* 2020; 9:2.
67. Missoum A. Recent Updates on Mesenchymal Stem Cell Based Therapy for Acute Renal Failure. *Curr Urol* 2020; 13:189-199.
68. Qian X, Xu C, Fang S, et al. Exosomal MicroRNAs derived from umbilical mesenchymal stem cells inhibit hepatitis C virus infection. *Stem Cells Transl Med* 2016; 5:1190-1203.
69. Gao L, Zhong X, Jin J, Li J, Meng XM. Potential targeted therapy and diagnosis based on novel insight into growth factors, receptors, and downstream effectors in acute kidney injury and acute kidney injury-chronic kidney disease progression. *Signal Transduct Target Ther* 2020; 5:9.
70. Hu J, Yu X, Wang Z, et al. Long term effects of the implantation of Wharton's jelly-derived mesenchymal stem cells from the umbilical cord for newly-onset type 1 diabetes mellitus. *Endocr J* 2013; 60:347-357.
71. Riordan NH, Morales I, Fernández G, et al. Clinical feasibility of umbilical cord tissue-derived mesenchymal stem cells in the treatment of multiple sclerosis. *J Transl Med* 2018; 16:57.
72. Dasari VR, Veeravalli KK, Dinh DH. Mesenchymal stem cells in the treatment of spinal cord injuries: A review. *World J Stem Cells* 2014; 6:120-133.
73. Daley GQ. The promise and perils of stem cell therapeutics. *Cell Stem Cell* 2012; 10:740-749.
74. Navani A, Manchikanti L, Albers SL, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22:S1-S74.
75. Sanapati J, Manchikanti L, Atluri S, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. *Pain Physician* 2018; 21:515-540.
76. Manchikanti L, Centeno CJ, Atluri S, et al. Bone marrow concentrate (BMC) therapy in musculoskeletal disorders: Evidence-based policy position statement of American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2020; 23:E83-E129.
77. Pean CA, Kingery MT, Strauss E, Bosco J, Halbrecht J. Direct to consumer advertising of stem cell clinics: Ethical considerations and recommendations for the healthcare community. *J Bone Joint Surg Am* 2019; 101:e103.
78. FTC stops deceptive health claims by a stem cell therapy clinic. Federal Trade Commission. October 18, 2018. Accessed date 3/18/2020.
www.ftc.gov/news-events/press-releases/2018/10/ftc-stops-deceptive-health-claims-stem-cell-therapy-clinic
79. Daley GQ. Polar extremes in the clinical use of stem cells. *N Engl J Med* 2017; 376:1075-1077.
80. FDA News Release. FDA acts to remove unproven, potentially harmful treatment used in 'stem cell' centers targeting vulnerable patients. Vaccinia Virus Vaccine (Live) seized after being used inappropriately in vulnerable cancer patients. August 28, 2017. Accessed date 3/18/2020
www.fda.gov/NewsEvents/Newsroom/

PressAnnouncements/ucm573427.htm.

81. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff, November 2017. Accessed date 3/18/2020.
www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
82. U.S. Department of Health and Human Services. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception. Guidance for Industry. November 2017.
www.fda.gov/downloads/BiologicsBlood-VaccinesdanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf Accessed date 3/18/2020.
83. U.S. Food and Drug Administration. Regenerative medicine advanced therapy designation. March 13, 2017. Accessed date 3/18/2020.
www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm
84. Murray IR, Chahla J, Frank RM, Piuzzi NS, Mandelbaum BR, Dragoo JL; Members of the Biologics Association. Rogue stem cell clinics. *Bone Joint J* 2020; 102-B:148-154.
85. Aicher RH. Is the FDA regulating the practice of medicine? *Aesthet Surg J* 2013; 33:452-455.
86. Charo A, Sipp D. Rejuvenating regenerative medicine regulation. *N Engl J Med* 2018; 378:504-505.
87. Malarkey MA. Warning letter to Thomas E. Young, MD, Owner and Medical Director, Young Medical Spa. Rockville, MD: Public Health Service, Food and Drug Administration; April 20, 2012. Accessed date 3/18/2020.
www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm301620.htm
88. Warning Letter to John S. Arnone, American CryoStem Corporation from Elizabeth Waltrip, Acting Program Division Director, Office of Biological Products Operations – Division 1, U.S. Food and Drug Administration. Accessed date 3/18/2020
www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm591225.htm.
89. Associated Press. North Darkota stem cell clinic investigated after complaints. *The Seattle Times*, November 16, 2017. Accessed date 3/18/2020.
www.seattletimes.com/nation-world/bismarck-stem-cell-clinic-investigated-after-complaints/
90. Kuriyan AE, Albini TA, Townsend JH, et al. Vision loss after intravitreal injection of autologous "stem cells" for AMD. *N Engl J Med* 2017; 376:1047-1053.
91. Malarkey MA. Warning letter to David G. Eller, Chief Executive Officer and President, Celltex Therapeutics Corporation. Rockville, MD: Public Health Service, Food and Drug Administration; September 24, 2012. Accessed date 3/18/2020.
www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm323853.htm
92. Schwarz A. New procedure uses athletes' own blood to treat injuries. *New York Times*, 2009, A1. Accessed date 3/18/2020.
www.nytimes.com/2009/ 02/17/ sports/17blood.html.
93. Piuzzi N, Ng M, Chughtai M, et al. The stem-cell market for the treatment of knee osteoarthritis: A patient perspective. *J Knee Surg* 2018; 31:551-556.
94. Turner L, Knoepfler P. Selling stem cells in the USA: Assessing the direct-to-consumer industry. *Cell Stem Cell* 2016; 19:154-157.
95. Government of Canada. Health Canada Policy Position Paper – Autologous Cell Therapy Products. Accessed date 3/18/2020.
www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/cell-therapy-policy.html
96. Chen S. Coronavirus: critically ill Chinese patient saved by stem cell therapy, study says. *South China Morning Post*, March 2, 2020. Accessed date 3/18/2020.
www.scmp.com/news/china/society/article/3053080/coronavirus-critically-ill-chinese-patient-saved-stem-cell
97. Liang B, Chen J, Li T, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. *ChinaXiv* 2020; 202002.00084.
98. China uses stem cell therapy to treat severe coronavirus cases. *Gulf News*, March 5, 2020. Accessed date: 3/15/2020.
https://gulfnews.com/world/asia/china-uses-stem-cell-therapy-to-treat-severe-coronavirus-cases-1.1583399782425
99. ClinicalTrials.gov. Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus. ClinicalTrials.gov Identifier: NCT04252118. Accessed date 3/15/2020.
https://clinicaltrials.gov/ct2/show/NCT04252118
100. ClinicalTrials.gov. Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia. ClinicalTrials.gov Identifier: NCT04269525. Accessed date 3/15/2020.
https://clinicaltrials.gov/ct2/show/NCT04269525?term=stem+cells&cond=Corona+Virus+Infection&draw=2
101. ClinicalTrials.gov. Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia. ClinicalTrials.gov Identifier: NCT04273646. Accessed date 3/15/2020.
https://clinicaltrials.gov/ct2/show/NCT04273646?term=stem+cells&cond=Corona+Virus+Infection&draw=2
102. ClinicalTrials.gov. Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus. ClinicalTrials.gov Identifier: NCT04293692. Accessed date 3/15/2020.
https://clinicaltrials.gov/ct2/show/NCT04293692?term=stem+cells&cond=Corona+Virus+Infection&draw=2&rank=7
103. Alcayaga-Miranda F, Cuenca J, Khoury M. Antimicrobial activity of mesenchymal stem cells: Current status and new perspectives of antimicrobial peptide-based therapies. *Front Immunol* 2017; 8:339.
104. Predictive Technology Group Addresses Use of Mesenchymal Stem Cells in Treatment of Secondary Issues Related to Coronavirus. GlobeNewswire, March 17, 2020.
https://finance.yahoo.com/news/predictive-technology-group-addresses-mesenchymal-154552966.html

105. Frew L, Stock SJ. Antimicrobial peptides and pregnancy. *Reproduction* 2011; 141:725-735.
106. Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. *J Leukoc Biol* 2004; 75:39-48.
107. Bals R, Weiner DJ, Moscioni AD, Meegalla RL, Wilson JM. Augmentation of innate host defense by expression of a cathelicidin antimicrobial peptide. *Infect Immun* 1999; 67:6084-6089.
108. Schneider JJ, Unholzer A, Schaller M, Schäfer-Korting M, Korting HC. Human defensins. *J Mol Med (Berl)* 2005; 83:587-595.
109. Krasnodembskaya A, Song Y, Fang X, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells* 2010; 28:2229-2238.
110. Sutton MT, Fletcher D, Ghosh SK, et al. Antimicrobial properties of mesenchymal stem cells: therapeutic potential for cystic fibrosis infection and treatment. *Stem Cells Int* 2016; 2016:12.
111. Hernigou P, Trousselier M, Roubineau F, et al. Stem cell therapy for the treatment of hip osteonecrosis: A 30-year review of progress. *Clin Orthop Surg* 2016; 8:1-8.
112. Arutyunyan I, Elchaninov A, Makarov A, Fatkhudinov T. Umbilical Cord as Prospective Source for Mesenchymal Stem Cell-Based Therapy. *Stem Cells Int* 2016; 2016:6901286.
113. Weiss ML, Trover DL. Stem cells in the umbilical cord. *Stem Cell Rev* 2006; 2:155.162.
114. Nagamura-Inoue T, He H. Umbilical cord-derived mesenchymal stem cells: Their advantages and potential clinical utility. *World J Stem Cells* 2014; 6:195-202.
115. Tipnis S, Viswanathan C, Majumdar AS. Immunosuppressive properties of human umbilical cord-derived mesenchymal stem cells: role of B7-H1 and IDO. *Immunol Cell Biol* 2010; 88:795-806.
116. Bauer G, Elsallab M, Abou-El-Enein M. Concise Review: A comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. *Stem Cells Transl Med* 2018; 7:676-685.
117. Rosenbaum L. Facing Covid-19 in Italy - Ethics, Logistics, and Therapeutics on the Epidemic's Front Line. *N Engl J Med* 2020 Mar 18. [Epub ahead of print]
118. French Gouvernement. Coming to France? Is it safe to come to France? Coronavirus COVID-19. March 18, 2020. Accessed date 3/20/2020
www.gouvernement.fr/en/coronavirus-covid-19.
119. French Gouvernement. Coronavirus COVID-19. March 18, 2020. Accessed date 3/20/2020.
www.gouvernement.fr/en/coronavirus-covid-19
120. Blum N. How Iran became a global vector of infection for COVID-19. *Tablet*, March 13, 2020. Accessed date 3/20/2020.
www.tabletmag.com/jewish-news-and-politics/middle-east/300948/iran-coronavirus-covid-19
121. Yamey G. What the U.S. needs to do today to follow South Korea's model for fighting coronavirus. *Time*, March 17, 2020. Accessed date 3/20/2020
https://time.com/5804899/u-s-coronavirus-needs-follow-s-korea/ .
122. Thacker T, Sharma N. COVID-19 in India: Cautious government involves private sector in treatment patients. *The Economic Times*, March 18, 2020. Accessed date 3/20/2020.
https://economictimes.indiatimes.com/industry/healthcare/biotech/healthcare/cautious-govt-involves-private-sector/articleshow/74681205.cms?from=mdr
123. Gostin LO, Hodge JG, Wiley LF. Presidential powers and response to COVID-19. *JAMA* 2020 Mar 18. [Epub ahead of print].
124. James S. Brady Press Briefing Room. Remarks by President Trump, Vice President Pence, and Members of the Coronavirus Task Force in Press Briefing. March 14, 2020. Accessed date 3/15/2020.
www.whitehouse.gov/briefings-statements/remarks-president-trump-vice-president-pence-members-coronavirus-task-force-press-briefing/