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Update on COVID-19 Infections and the Promising Role of Mesenchymal Stem Cell Therapies in their Management

Subject Category: Stem Cell Therapy

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Abstract

The pandemic of COVID-19 has adversely affected almost every aspect of our lives but the world health and economic sectors suffer most of the repercussions of this disease. The search for a cure for this rapidly spreading virus which is causing massive life losses around the globe requires clear understanding of the immunopathogenesis of this virus as well as the mechanisms of actions of the various therapeutic modalities that are employed in the treatment of this life-threatening viral infection. Mesenchymal stem cells have antimicrobials effects in addition to their anti-inflammatory and immunomodulatory properties. They have been utilized in the treatment of various infections and their complications both in animal models and in human clinical trials. Mesenchymal stem cells derived from certain sources and their secretory products are particularly effective in the treatment of pneumonia, sepsis, acute lung injury, and acute respiratory distress syndrome which are common complications of COVID-19 infections. The review will discuss the various aspects of COVID-19 and it will highlight the promising role of mesenchymal stem cells in treating the complications of COVID-19 infections.

Keywords

COVID-19, Pneumonia, Aute respiratory distress syndrome, Acute lung injury, Mesenchymal stem cells, Secretome, Umbilical cord blood, Adipose tissue

Introduction

In late December 2019, an unprecedented outbreak of pneumonia that was caused by a novel betacoronavirus emerged in Wuhan City in China. On February 11, 2020, the new corona virus was named severe acute respiratory syndrome CoV-2 (SARS-CoV-2) and the illness caused by this novel coronavirus was called coronavirus disease 2019 (COVID-19) by the world health organization (WHO) [1-7]. SARS-CoV-2 virus spreads faster than its 2 ancestors; the SARS-CoV and the Middle East respiratory syndrome (MERS-CoV); which caused respiratory tract infections in China and Saudi Arabia in the years 2002 and 2012 respectively, but SARS-CoV-2 has lower case fatality rates than the other 2 coronaviruses [1,4,8,9]. The WHO declared the Chinese outbreak a public health emergency with international concerns on January 30, 2020 and then it declared COVID-19 a pandemic on March 11, 2020 [1-3,10]. The current disease pandemic has already caused massive life losses all over the globe. Additionally, it has practically disturbed almost every single aspect of life and its repercussions have adversely affected world economy [2,11,12]. Clinically, patients with COVID-19 present predominantly with fever and respiratory manifestations and less frequently with gastrointestinal symptoms. However, the illness may be complicated by severe pneumonia, acute respiratory distress syndrome (ARDS), and respiratory failure that may be followed by multiorgan failure and death [2,5,6,8,11,13].

Currently, there is no licensed specific antiviral treatment and a vaccine is not yet available for COVID-19 [10,14-16]. The available therapeutic interventions include: (1) symptomatic measures and supportive care; (2) oxygen supplementation, non-invasive ventilation, endotracheal intubation, and mechanical ventilation; (3) management of septic shock and secondary bacterial infection; (4) drug repurposing using mainly antiviral agents, anti-inflammatory drugs, and monoclonal antibodies; and (5) other therapeutic measures including: use of convalescent plasma, removal of cytokines and blood purification, Chinese traditional medicines, and cellular therapies [4,6,11,13,17]. However, combination of 2 or more therapeutic modalities appears to be more successful in the management of COVID-19 than the use of single agents [6,11,18].

Mesenchymal stem cells (MSCs) have antimicrobial as well as immunomodulatory properties and they have been used, with variable success rates, in the treatment of several infectious diseases both in animal models and in human clinical trials [19-21]. MSCs derived from umbilical cord (UC) tissues appear to be more advantageous than other sources of MSCs [22-25]. Recently, MSC-secretomes have been shown to be superior to pure cellular therapies [26-28]. MSCs and their secretory products have shown promising results in the treatment of sepsis, viral pneumonia, acute lung injury (ALI), and ARDS [21,29,30]. Since January 2020, several reports have been published on the success of MSC therapies in the treatment of COVID-19 and this illustrates their promising potential in the management of COVID-19 infections in conjunction with other therapeutic modalities [31-34]. Interestingly, treatment of COVID-19 pneumonia with MSCs can suppress the associated cytokine storm [20,29,33,34].

Viral Aspects and Immunopathogenesis

Viral aspects of COVID-19

In late December 2019, a patient presented to the Central Hospital in Wuhan, China with severe respiratory syndrome that included fever, dizziness and cough. After subjecting the bronchoalveolar lavage (BAL) samples taken from the patient to metagenomics RNA sequencing a new RNA virus belonging to the family *Coronaviridae* was identified, then its complete viral genome that was composed of 29,903 nucleotides was described [35]. Following the first release of SARS-CoV-2 genome, public health and research laboratories have rapidly shared the sequences on public data repositories, such as the global initiative on sharing all influenza data (GISAID), which have been used to provide quick or snapshots of global diversity through public analytic and visualization tools [36]. As of March 23, 2020; 558 SARS-CoV-2 isolates from different regions in the world have been genotyped and frequent mutations in the genes encoding the S protein, RNA polymerase, and nucleoprotein have been described [37].

The continuous emergence and re-emergence of pathogenic viruses, which have potentially global catastrophic consequences such as COVID-19, has become a major threat to public health worldwide [38]. A database of 319 viral genes, that can discriminate overlapping from non-overlapping genes with accuracy close to 100%, has been assembled. This database may be crucial to detect new overlapping genes in the genome of SARS-CoV-2 virus [39]. Knowledge of the various genetic mutations involving the genome of SARS-CoV-2 is critical for the development of effective drugs and vaccines [37,40].

SARS-CoV-2 genome encodes 4 structural proteins: spike (S); envelope (E); membrane protein (M); and nucleoprotein (N) which are involved in various viral processes including formation of the virus particle [37,40]. New technologies that are being utilized in emerging infectious diseases play a major role in the: diagnosis of specific diseases, manufacture of vaccines, and rapid development of human monoclonal antibodies [41]. The following technologies are being utilized for detection of SARS-CoV-2 virus and its genetic mutations: whole genome sequencing (WGS), metagenomics RNA sequencing, reverse transcriptase polymerase chain reaction (RT-PCR), and genome detective coronavirus typing [35,36,38,42].

Pathogenesis of COVID-19

The pathogenesis of COVID-19 involves the following: (1) immune-mediated mechanisms; (2) direct cytotoxic mechanisms; (3) involvement of antibody-dependent enhancement which is a cascade of events whereby a virus may infect susceptible cells by interaction between virion complexes and antibodies or complement components leading to amplification of viral replication; (4) viral sepsis as many critically ill COVID-19 patients develop typical clinical manifestations of septic shock such as hypotension, cold extremities, and weak peripheral pulses; (5) severe pneumonia with ground glass opacities, ARDS, respiratory failure followed by multiorgan failure; and (6) cytokine storm with significant elevation of proinflammatory cytokines such as: interleukin (IL)-2, IL-7, IL-10, granulocyte-monocyte colony stimulating factor (GM-CSF), G-CSF, vascular endothelial growth factor A, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ [1,43-45]. The major virus-host interactions that occur in COVID-19 infection include: delayed or suppressed type 1 IFN response during initial infection, viral replication which triggers hyperinflammatory condition, influx of activated neutrophils, inflammatory monocytes and macrophages, induction of TH1/TH17 and production of specific antibodies [45].

The different clinical presentations of COVID-19 depend on the interaction between the following factors: (1) severity of infection, host response, physiological reserve and comorbidities; (2) the ventilator responsiveness of the patient to hypoxia; and (3) the time that elapses between onset of disease and observation in hospital. Consequently, two primary disease spectra or phenotypes are usually observed: (1) type L which is characterized by low levels of: elastase, ventilation:perfusion ratio, lung weight, and recruitability; and (2) type H which is characterized by high levels of: elastase, right to left shunt, lung weight, and recruitability [46]. Immunopathologically, the following changes have been reported in patients with COVID-19: (1) reduction in the blood counts of lymphocytes and natural killer cells (NKCs); (2) impairment or destruction of the immune system with atrophy of lymph nodes and spleen; (3) inflammatory cytokine storm or extremely high inflammatory parameters including C-reactive protein (CRP), and the proinflammatory cytokines: IL-6, IL-8, and TNF-α; (4) the majority of infiltrated immune cells in lung lesions are monocytes and macrophages with minimal lymphocyte infiltration; and (5) minimcry of vasculitis, hypercoagulability with thrombosis, and damage of

multiple organs [47]. The possible or hypothetical mechanisms of pathogenesis include: (1) the virus may pass through mucous membranes of the nose and larynx, then it enters the lungs through the respiratory tract; (2) the virus may enter the peripheral blood (PB) from the lungs causing viremia; (3) the virus may attack target organs that express angiotensin converting enzyme 2 (ACE 2) such as lungs, heart, kidneys and gastrointestinal tract (GIT); and (4) the virus begins a second attack causing the condition of the patient to worsen around day 7-14 from the onset of the infection. Consequently, the clinical condition of the patient may take one of 2 routes: (a) if the immune function of the patient in the acute phase of pneumonia is effective, no more complications occur and the patient is likely to enter the recovery phase as the virus is sufficiently suppressed by the immune system of the host; and (b) if the patient is old or has an immunocompromising illness such as cancer or diabetes mellitus (DM), the immune system of the host can't effectively control the virus in the acute phase, so the patient is likely to deteriorate further and enter the critical stage [48].

Entry of the virus into cells which is mediated by the S glycoprotein (spike) following binding to ACE-2 requires the presence of the protease furin to promote entrance of the virus into the cells, and involves Notch signaling pathway which is involved in the regulation of furin and ADAM-17. Hence, targeting the following may become an effective therapeutic modality for COVID-19 infection: ACE-2, Notch signaling, and IL-6 which is involved in the cytokine storm [49].

SARS-CoV-2 infects lung alveolar epithelial cells by receptor-mediated endocytosis in association with ACE-2 [50,51]. The main target of COVID-19 is the epithelium of the respiratory system, but SARS-CoV may directly attack cardiomyocytes and subsequently cause viral myocarditis and cardiac decompensation [50-52]. Causes of cardiac dysfunction in COVID-19 include: pulmonary dysfunction, ARDS, pulmonary embolism, hypotension, shock, hypoxia, respiratory and metabolic acidosis, electrolytic disturbances, enhanced inflammatory status with downregulation of ACE-2 receptors; as well as activation of neuro-hormonal system following severe infection and these abnormalities may lead to cardiac injury, malignant arrhythmias, and sudden death [50,52,53]. Myocardial injury associated with COVID-19 can be explained by: direct infection through ACE-2, imbalance between myocardial oxygen supply and demand, and the presence of an abnormal immune response [50-52]. Binding between SARS-CoV spike protein and ACE-2 on the surfaces of cardiomyocytes triggers the Ras-ERK-AP-1 pathway and activates the C-C motif chemokine ligand-2 (CCL2) to cause cardiac dysfunction and cardiac fibrosis [50].

Immune Cells in COVID-19

Neutrophils: Neutrophils are: the most abundant leukocytes in the peripheral circulation; essential players in host defense against invading pathogens; and the first cells to migrate to the sites of infection in order to execute their sophisticated functions that include killing microorganisms by phagocytosis and NETosis which is the release of neutrophil extracellular traps (NETs) [54-60]. In response to infection, neutrophils are recruited to the sites of infection and they employ the following 3 major strategies to fight various microbes: phagocytosis, degranulation, and NETosis [61-63]. During infection, neutrophils can undergo beneficial suicide resulting in the release of NETs to combat invasion by pathogens [59]. During overwhelming infections and severe sepsis, neutrophils become dysfunctional or paralyzed and their antimicrobial arsenal may contribute to further tissue damage and organ failure as the host becomes unable to contain or eliminate the infection [54,64-67]. Consequently, in severely immunocompromised individuals with neutropenia having severe sepsis and overwhelming infections, host immunity can be boosted further by donor granulocyte transfusions and intravenous (IV) immunoglobulins [68-71].

Recent studies have shown that neutrophils: (1) may differentiate into distinct subsets defined by specific phenotype and functional profile under certain circumstances; (2) can exhibit reverse transmigration and reenter the circulation after shifting their phenotype towards a proinflammatory state with longer life span of about 5.4 days; and (3) are involved in: (a) activation, maturation, and the complex bidirectional crosstalk with macrophages, T-lymphocytes, NKCs, MSCs, platelets, and B-lymphocytes, monocytes and dendritic cells (DCs), and (b) regulation of T-cell immune responses against various pathogens [71-76]. Neutrophils are capable of recognizing viruses via viral pathogen-associated molecular patterns (PAMPs) and they respond to viruses with certain effector functions [77]. The cytokines that are produced by leukocytes and induced by PAMPs include: TNF-α, IL-6, and IL-1 components [78,79]. Hence, neutrophils may be key elements in determining the outcome of viral disease [78,80].

NETs are extracellular structures composed of chromatin and granule proteins that bind and kill microorganisms and they arise from neutrophils that have activated a cell death program called NETosis or NET cell death [81-83]. NET formation can be influenced by: (1) microorganisms including viruses and bacteria; (2) cytokines such as TNF-α and IL-

8; (3) antimicrobials including amoxicillin; and (4) chemicals such as calcium ionophore A23187 and phorbol myristate acetate [56,59,84]. NETs can inactivate virulence factors or microbial proteins that modify the function of host cells [63,85]. NETs have several antimicrobial actions, but they have a dark side reflected by their involvement in certain disorders including: (1) autoimmune disorders such as systemic lupus erythromatosis; (2) preeclamsia associated with pregnancy; (3) coagulopathy and thrombosis; (4) cystic fibrosis; (5) periodontitis; and (6) tissue injuries [56,59,60,63,86-92]. Excessive NET formation can trigger a cascade of inflammatory reactions that can facilitate microthrombi and result in permanent damage to the pulmonary, cardiovascular and renal systems. Additionally, in patients with DM, hyperglycemia induces NET formation and this may cause direct damage to endothelial cells and predispose to complications such as diabetic retinopathy and diabetic wounds [56,90,91].

Recently, it has been shown that viruses can trigger the process of NETosis [93-96]. Virus-induced NETosis can ensure mechanical entrapment of the virus, but may cause harm by the release of NETs as virus-induced NETs can lead to extreme systemic response manifested by production of cytokines, chemokines, and immune complexes that favor inflammation [93]. COVID-19 patients may have leukocytosis or leukopenia and high neutrophil:lymphocyte ratio (NLR), the latter being considered an independent risk factor for disease severity, poor clinical outcome, and mortality [97-100].

NETosis, which represents the most dramatic stage in the process of cell death, is a recently described neutrophil function that leads to the release of NETs in response to various stimuli [57,60]. In patients with COVID-19, high levels of NETs have been documented and NETosis may be responsible for many of the serious complications associated with COVID-19 including: ARDS, respiratory failure, cytokine storm, thromboembolic complications, and acute organ dysfunction that leads to multiorgan failure [93,101-103]. Thus, targeting NETs directly or indirectly with the existing drugs may reduce the clinical severity of COVID-19 infection [104]. Additionally, treatments that inhibit viral replication or target regulation of the dysfunctional immune reactions may offer synergistic effects to block viral pathologies at multiple levels [17].

DCs: DCs are the key regulators of immune response. They are professional antigen presenting cells that link innate and adaptive immunity and they have important roles in immune surveillance, priming and tolerance [105]. SARS-CoV can infect mature and immature DCs and cause impairment of their function that can manifest as: low expression of antiviral cytokines, moderate upregulation of proinflammatory cytokines, and significant upregulation of inflammatory chemokines [106-108]. MERS-CoV could productively infect monocyte-derived DCs and this infection can result in: excessive production of cytokines and chemokines, and modulation of the innate immune response. Thus, DCs serve as a new target of viral replication of certain coronaviruses [109].

NKCs: NKCs represent the first line of defense against viral infections and they play a central role in killing virus-infected cells [110,111]. Viral infections may affect the proliferation of NKCs causing dysfunction of these cells [111,112]. Virus-induced IFN activates NKCs to become highly cytotoxic [112]. NKCs recognize and kill virally-infected cells by: (1) spontaneous cytolytic activity or direct killing of virus-infected cells to rapidly control viral infection, and (2) secretion of a variety of immune or soluble mediators such as IFN-γ and other cytokines [110,111]. NK cytotoxicity is regulated by several receptors including CD158b that binds to major histocompatibility complex class I molecules on target cells. NKCs are also involved in the pathogenesis of SARS [110]. The number of NKCs decreases at the onset of SARS then decreases further during the second week of infection. Later on, they start increasing, although not reaching normal levels, with the recovery from SARS [113].

B-cells, T-cells, Monocytes/Macrophages: The level of B-lymphocytes increases during the second week of SARS and keeps increasing till it normalizes in the 5th week of infection [113]. The effector memory Vγ9Vδ2T cells play a protective role during SARS and may release type II IFN. Therefore, Vγ9Vδ2T cells can be employed in the management of SARS by utilizing their interferon secretion [114].

SARS-CoV poorly infects human peripheral blood PB and macrophages. PB monocytes and macrophages produce IFN-α which helps in limiting the viral infection [115]. Two clinical trials on the use of NKCs, one NKCs alone and one NKCs in combination with MSCs, have been registered for the treatment of COVID-19 [29]. On Apr 2, 2020; Cellularity announced food and drug administration (FDA) approval of the use of allogeneic cryopreserved NKCs in the treatment of COVID-19 [116].

The Benefits of leukemia inhibitory (LIF) factor in COVID-19

LIF belongs to the IL-6 family of cytokines [117-119]. Several studies have shown that in patients with severe lung

infection and septic shock: (1) high circulating levels of LIF have been reported, and (2) LIF could protect the lung from further injury during pneumonia due to its tissue protective effects [117,118,120-122]. LIF has also been found to enhance endogenous cardiomyocyte regeneration following myocardial infarction. Such tissue regenerative effect may be useful in patients with COVID-19 pneumonia who develop cardiac decompensation [119,122].

The Role of ACE-2 in COVID-19

The renin-agiotensin system (RAS) is crucial for the physiology as well as pathology of all body organs [123]. The cell receptor ACE2 which is the key enzymatic component of the renin-angiotensin-aldosterone system maintains the homeostasis of RAS by negative regulation [123,124]. ACE2 regulates blood pressure and amino acid absorption in the GIT and kidneys and modulates the expression of amino acid transporters [123]. ACE2 is expressed in various tissues and body organs including: lungs, heart, GIT, liver, kidneys, and brain [123,124].

SARS-CoV-2 virus uses ACE2 as a cell receptor to invade human cells because the virus must bind to ACE2 before entering the human host cells [123,125-131]. So, ACE2 is the key to understand the mechanism of SARS-CoV-2 virus infection and may be essential in the progression and clinical outcome of COVID-19 [123,131]. The receptor binding domain of the surface glycoprotein (S protein) of SARS-CoV-2 is recognized by the extracellular peptidase domain of ACE2 mainly through polar residues [128]. ACE2 expression has been found to be elevated in cigarette smokers and this possibly makes chronic cigarette smoking as a risk factor for COVID-19 infection [130]. Also, ACE2 expression on the surface cell of the small intestine may mediate the invasion and amplification of the virus and activation of GIT inflammation and it may explain the presence of SARS-CoV-2 virus in the stool samples of patients with COVID-19 infection [132]. Recognition that ACE2 is the receptor for coronavirus has prompted the search for new therapeutic approaches to block the enzyme and reduce its expression to prevent cellular entry and infiltration of SARS-CoV-2 virus in tissues that express ACE2 [124].

The use of ACE inhibitors in older patients with DM and hypertension leads to an increase in the expression of ACE2 thus making the cells more vulnerable to infection with SARS-CoV-2 virus [125,126]. The use of ACE inhibitors and angiotensin-receptor blockers (ARBs) may provide cardiovascular and renal protection in patients with COVID-19 [133,134]. ACE inhibitors and ARBs should be continued in patients with cardiovascular disease and hypertension having COVID-19 infection as discontinuation of these medications may be potentially harmful in this patient population [129,133].

Using classical molecular dynamics simulation, it has been shown that peptide inhibitors extracted from ACE2 provide highly promising trails for blocking SARS-CoV-2 virus [127]. There is growing body of evidence suggesting that: (1) the pathogenesis of COVID-19 pneumonia resembles that of autoimmune inflammatory disorders; (2) the genetic host characteristics, such as IL-6 polymorphisms, may contribute to the virus susceptibilities in specific populations and ethnicities; and (3) ACE2 could be the direct link between SARS-CoV-2 virus infection and the development of lung injury and severe inflammation [135-137]. Patients receiving ACE inhibitors and ARBs have been found to have: (1) lower rates of severe COVID-19 infection; (2) a trend towards a lower level of IL-6 in peripheral blood; (3) elevated CD3+ and CD8+ T-cell counts in PB; and (4) decrease in the peak viral load compared to patients receiving other antihypertensive medications. Thus the use of ACE inhibitors and ARBs might have potentially contributed to the improvement in clinical outcomes encountered in hypertensive patients having COVID-19 infections [134].

Clinical aspects and complications of COVID-19

There are several risk factors for acquiring COVID-19 infection and these include: old age; comorbid medical conditions such as DM, hypertension, chronic kidney diseases; chronic lung disease such as bronchial asthma, cardiovascular disorders and cerebrovascular diseases; cigarette smoking; cancers including solid tumors and hematologic malignancies; recipients of solid organ as well as hematopoietic stem cell transplantation (HSCT); and pregnancy [138-150]. Clinical suspicion is made on the basis of having: (1) relevant clinical manifestations; (2) history of (H/O) travel to a country or a town having cases of COVID-19 infections; and (3) H/O contact with infected person should initiate viral assays and early radiological imaging [151]. The clinical manifestations of COVID-19 are shown in table 1 [2,5,6,11,148,151-162].

The incubation period of COVID-19 ranges between 2 and 14 days [2,5,154,163]. SARS-C0V-2 can be transmitted by the following means: respiratory droplets, direct contact, and possibly oral-fecal route as virus has been detected in the stools [154,164]. SARS-CoV-2 virus has powerful capacity to replicate in host cells by inhibiting antiviral immune responses. Hence, transmission of COVID-19 is influenced by host-related factors that are linked to immune dysregulation and examples include: old age is associated with immune dysregulation and reduction in T-cell repertoire, male gender is associated with reduced antiviral immunity, and medical comorbidities are associated with severe inflammation [165]. However, recurrence of COVID-19, although rare, may be encountered [164].

Systemic complications of COVID-19

Hematological complications: SARS-CoV may cause thrombocytopenia and lymphopenia by: autoimmune antibodies or immune complexes triggered by the viral infection and direct infection of hematopoietic stem/progenitor cells via CD13 or CD66a, thus causing growth inhibition and apoptosis. CD13 has been identified in human bone marrow (BM) CD34+ cells [166,167]. CD66a is an adhesion molecule which is expressed on CD34+BM cells, platelets, granulocytes and activated lymphocytes. Additional causes of thrombocytopenia in SARS-associated lung damage include: increased consumption and reduced production of platelets [166,167].

However, the hematological complications of COVID-19 include: neutrophilia or neutropenia; lymphopenia that may be severe and persistent with functional exhaustion of cytotoxic lymphocytes; normocytic anemia; monocytopenia or mild monocytosis; thrombocytopenia; low eosinophil and basophil counts; leucoerythroblastic blood picture; decrease in PB CD4+ and CD8+ T-lymphocytes; high neutrophil:lymphocyte ratio; high monocyte:lymphocyte ration; disseminated intravascular coagulation (DIC); venous thromboembolism such as deep vein thrombosis (DVT); arterial thrombosis such as pulmonary embolism, cerebral infarction and acute myocardial infarction [99,155,168-174]. In patients with COVID-19, thrombocytopenia is associated with severe disease and increased mortality [173].

Table 1: Clinical manifestations and complications of COVID-19.

- Fever
- Cough
- Fatigue
- Shortness of breath
- Rhinorrhea
- Hemoptesis
- Chest pain
- Nausea, vomiting, diarrhea, and abdominal pain
- Muscle aches
- Loss of smell and taste sensations
- Headache
- Mental confusion
- Conjunctival injection
- Severe pneumonia
- Acute respiratory distress syndrome and respiratory failure requiring mechanical ventilation.
- Acute cardiac decompensation, arrhythmias, and heart failure.
- Acute renal and liver dysfunction.
- Multiorgan failure
- Thromboembolism: deep venous thrombosis, pulmonary embolism, myocardial infection, and cerebral stroke.
- Septic shock
- Secondary bacterial infection.
- Death

COVID-19 may predispose to venous and arterial thrombosis due to: excessive inflammation, hypoxia, immobilization, and DIC [168]. Severe COVID-19 may also cause a catastrophic microvascular injury mediated by activation of complement pathways and an associated procoagulant state [175]. Hence, prophylactic anticoagulation is recommended for intensive care unit (ICU) patients with COVID-19 [168,176]. In patients having evidence of thrombosis, anticoagulant therapy is recommended in the absence of contraindication to anticoagulation. However, parenteral anticoagulant drugs are preferred with choice of drug and dosage depending upon the location and severity of the thromboembolism [155]. Patients with COVID-19 are likely to develop DIC blood picture: low platelets, prolongation of prothrombin time and activated partial thromboplastin time, elevated D-Dimer and fibrin degradation products [177]. Patients with COVID-19 are at risk of developing the following thromboembolic complications: DVT, pulmonary embolism, acute MI, and cerebral infarction [155].

A novel COVID-19 associated pulmonary vasculopathy or pulmonary intravascular coagulation (PIC) has recently been described by Fogarty H. et al, and it is manifested by: disseminated microthrombi in lung microcirculation, and significant hemorrhagic necrosis in lung tissues. However, ethnicity and race have major effects on the risk of thrombosis as it has been shown that the thromboembolic episodes are higher in Caucasians and black Americans than in the Chinese [176].

Hepatic and GIT complications of COVID-19: The following hepatic complications have been described in patients with COVID-19: acute hepatitis; fulminant hepatic failure; elevated aspartate aminotransferase, alanine aminotransferase, and Gamma-glutamyl transferase; and low albumin. Histologically, COVID-19 causes: apoptosis of liver cells, eosinophilic bodies, balloon-like hepatocytes, and presence of viral particles in parenchyma and vascular endothelium of the liver [178,179].

Studies have shown that more than 10% of patients with COVID-19 present with GIT manifestations such as nausea, vomiting and diarrhea and that these symptoms may precede respiratory manifestations [180-182]. SARS-CoV uses the ACE 2 and the serine protease TMPRSS2, which is expressed in the epithelium of small intestine and not in the lung. Also, shedding of corona RNA viruses may be detectable in the stools earlier than in nasopharyngeal swabs indicating a possible oral transmission [181,182].

Neurological and muscular complications; Neurological complications associated with coronaviruses include: anosmia, myositis, meningitis, encephalitis, post-infectious acute disseminated encephalomyelitis and brain stem encephalitis, acute necrotizing hemorrhagic encephalopathy, and Guillain-Barre syndrome [125]. However, COVID-19 has the following neurological complications: (1) central nervous system: headache, dizziness, impaired consciousness, ataxia, cerebral infarction, epilepsy, and coma; (2) peripheral nervous system: neuralgia, hyposia, hyposmia, and hypognesia; and (3) skeletal muscle symptoms: myalgia, myositis, and rhabdomyositis [125,155,183].

Renal complications; COVID-19 causes acute renal failure manifested by: proteinuria, hematuria, elevated serum levels of urea and creatinine, hyperkalemia, hyperuricemia, metabolic acidosis, reduced glomerular filtration rate, and renal hypoperfusion due to hypovolemia and sepsis. Pathological mechanisms involved in renal dysfunction associated with COVID-19: renal hypoperfusion, renal tubular toxicity, renal medullary hypoxia, septic acute kidney injury (AKI), renal compartment syndrome, cardiorenal syndrome type1, and direct effects of cytokine release [184,185].

AKI can be due to one or more of the following: cytokine damage due to cytokine release syndrome (CRS), organ crosstalk or effect of dysfunction or failure in other body systems or organs, and systemic effects of infection and inflammation [185]. In patients with AKI caused by COVID-19, CRS is multifactorial: increase levels of IL-6 caused by the infection; and additional causes such as: extracorporeal membrane oxygenation, invasive mechanical ventilation, and continuous kidney replacement therapy [185]. In a case series that included 5 patients on maintenance hemodialysis for end-stage renal disease who acquired COVID-19 infection, none of the patients developed severe complications such as ARDS, multiorgan failure, shock or death [186].

Cardiac complications; COVID-19 causes acute myopericarditis manifested by: hypotension, diffuse ST segment elevation, circumferential pericardial effusions, arrhythmias, severe left ventricular (LV) dysfunction, increase wall thickness with diffuse biventricular hypokinesia, marked biventricular myocardial interstitial edema, elevated serum lactate dehydrogenase level, and increased serum troponin-1 level [49,50,155,187,188]. Other cardiac complications that have been reported in patients with COVID-19 include: acute myocardial infarction with or without obstructive

coronary artery disease, decompensated heart failure, refractory cardiogenic shock, evidence of biventricular failure by echocardiography, cardiac arrest, and sudden death [49,50,189,190]. In patients with COVID-19, cardiac injury is associated with severe disease, ICU admission and higher mortality [189].

COVID-19 in pregnancy

Pregnant ladies are more susceptible to COVID-19 infection as well as pneumonia than general population or non-pregnant females [146,147]. COVID-19 may alter the immune response at the maternal-fetal interphase thus affecting the well-being of both the mother and the infant [147]. In pregnant females, COVID-19 infection may cause cardiomyopathy manifested by cardiac dysfunction, reduced LV ejection fraction, and hypokinesia [191]. COVID-19 has the following adverse effects on the outcome of pregnancy: preterm birth which is the most common complication; miscarriage; preeclampsia; and perinatal death [192]. Pregnancy is considered a risk factor for severe morbidity and mortality in COVID-19 infection [147]. Surprisingly, one retrospective study that included 9 pregnant females with COVID-19 pneumonia, who underwent Caesarean section in the third trimesters of their pregnancies reported no mortality or severe morbidity neither in the pregnant females nor in their offspring [146]. Studies have shown that there is no evidence or published cases of intrauterine vertical transmission of COVID-19 infection from mother to infant [146,147,192].

Asymptomatic Cases and Carriers

It is estimated that approximately 80% of cases of COVID-19 are asymptomatic and these asymptomatic cases might have been the source of infection in the documented cases of infection [160,193-195]. The relatively high proportion of asymptomatic or undocumented infection can explain the rapid geographic spread of COVID-19 and this may add to the challenges in containing the pandemic [193,194]. Presence of high proportion of asymptomatic cases or carriers of COVID-19 represents a high potential for spread of infection in the population and highlights the importance of: tracing close contacts, longitudinal surveillance via nucleic acid tests, and public health strategies taken to prevent spread of infection to hospitalized patients, health care workers, and relatives of patients having COVID-19 infection [196-199].

Clinical Stages or Phases of COVID-19 Infection

The following 3 distinct stages of phases of COVID-19 infection have been recognized: (1) stage I: symptomatic phase with viremia and it includes the initial 1-2 days of the illness or the incubation period with or without detectable virus; (2) stage II: acute but non-severe symptomatic period with the presence of the virus while the response of upper and lower airways to infection may take the form of pneumonia; and (3) stage or phase III: either clinical recovery or severe respiratory symptomatic stage with high viral load manifested by deterioration of the patients with hypoxia, ground glass pulmonary infiltrates, with progression into ARDS in one third of cases [48,200-203].

Definition of Severe or Critical Infections

Patients with severe COVID-19 need to be: identified early, closely observed, and given particular attention as they may need higher levels of care and additional therapies including immunotherapeutic interventions [202,203]. In China where COVID-19 started, the diagnosis of severe or critical infection is made when a patient meets the criteria established by the diagnosis and treatment scheme issued by the National Health Commission in China. Severe infection has the following criteria: (1) respiratory rate > 30 breaths/minute with dysnea; (2) blood oxygen saturation < 93% in resting state; (3) ratio of arterial oxygen partial pressure : fractional inspired oxygen < 300 mmHg; and (4) radiological evidence of foci in multiple lobes or > 50% progression of lung inflammation. However, critical infection is defined by the following criteria: (1) respiratory failure requiring mechanical ventilation; (2) shock; and (3) multiple organ failure and admission to ICU [162,202,203]. Factors that are associated with severity, disease progression and mortality are shown in table 2 [99,141-143,145,147,149,150,171-173,188,189,204-214].

Mortality and Case Fatality Rates

Initially mortality rates were high, reaching 11%-15% in hospitalized patients. Later on, death rates came down to 2%-3%. In most of the studies, mortality rates range between 0.47% and 3.4% [152-154]. Case fatality rates vary according to age. In patients < 60 years they range between 0.145% and 0.631%, while in patients ≥ 60 years, they range between 3.28% and 5.96% [215]. For all age groups, case fatality rates range between 1.3% and 2.6%, while in patients ≥ 70 years, they range between 6.4% and 13% [216]. So, case fatality rates increase with the advancement of age. Additionally, recurrence of COVID-19 infection has been reported [215-216].

Laboratory Aspects and Diagnosis of COVID-19

Laboratory and Radiological Diagnosis

Specimens can be obtained from: sputum, nasopharyngeal swabs, and bronchoalveolar lavage then one of the following tests can be performed: RT-PCR on the specimen taken, nucleic acid amplification test, and reverse transcription loop-mediated isothermal amplification [217]. The diagnosis of a confirmed case of COVID-19 should be based on the following: (1) positive RT-PCR for SARS-CoV-2; (2) viral WGS showing high heterogeneity to the known novel coronavirus; and (3) positive specific IgM antibody or IgG antibody to SARS-CoV-2 in the serum or a change in specific IgG antibody from negative to positive or a titer rising ≥ 4 times in the recovery phase above that in the acute phase [50].

Chest X ray (CXR) and computerized axial tomography (CAT) scans of lungs can be done. The following radiological findings which may be unilateral or bilateral can be encountered: parenchymal consolidation, multiple ground glass opacities, nodular infiltration, and pleural effusions. However, in rare cases CXR may be entirely normal [151].

Histological Findings in COVID-19 Infection

The following histopathological findings have been reported in the lungs of COVID-19 patients: (1) diffuse alveolar damage with proteinaceous exudates and edema formation; (2) focal hyperplasia of type II pneumocytes; (3) focal or patchy inflammatory cell infiltration with predominance of lymphocytes; (4) presence of multinucleated giant cells; (5) intra-alveolar hemorrhage; (6) abundant intra-alveolar neutrophilic infiltration in case of secondary bacterial infection; (7) hyaline membrane formation may or may not be present; (8) no definitive viral inclusions; and (9) PIC with diffuse microthrombi in pulmonary microvasculature and hemorrhagic necrosis involving lung tissues [50,176,218-220].

In patients with cardiac involvement, the following histopathological changes have been described: mild and focal pericardial edema, mild interstitial mononuclear cell infiltration, interstitial fibrosis, and myocardial hypertrophy [50,218]. In COVID-19 patients having liver involvement, the following abnormalities have been reported: sinusoidal dilatation, patchy hepatic necrosis in periportal and centrilobular areas, mild lymphocytic infiltration in sinusoids and portal tracts, and kupffer cell hyperplasia in focal sinusoids [218].

Table 2: Factors associated with severity, disease progression, poor prognosis and mortality in COVID-19.

1. Age: more than 60 years.
2. Male gender
3. Comorbid medical conditions:
    - a- Diabetes mellitus.
    - b- Hypertension and cardiovascular disease.
    - c- Cancer including hematologic malignancies..
    - d- Solid organ transplantation.
    - e- Pre-existing lung disorders.
4. Pregnancy.
5. Cigarette smoking
6. Severe disease manifested by expectoration and muscle aches.
7. Evolution of acute cardiac injury: myocardial infection, cardiogenic shock, and decompensated cardiac failure.
8. High SOFA (sequential organ failure assessment) score.
9. Hypoxemic respiratory failure requiring mechanical ventilation.
10. Hypotension or sepsis during the course of the infection.
11. Leukocytosis or neutrophilia.
12. Lymphopenia.
13. Thrombocytopenia.
14. Elevated D-Dimer > 1μg/L.
15. Elevated serum creatinine level.
16. Elevated C-reactive protein (CRP).
17. High creatinine kinase level.
18. High lactate dehydrogenase level.
19. Low serum albumin.
20. High neutrophil : lymphocyte ratio.
21. Low lymphocyte : CRP ratio.
22. High fibrinogen : albumin ratio.
23. Elevation of the following cytokines: interleukin (IL)-6, IP-10, MCP-3, HGF, MIG, and MIP-1α.
24. Alterations in T-lymphocyte subsets:
    (a) In CD4+ T-cells: low interferon (IRF)-γ and low tumor necrosis factor (TNF)-α
    (b) In CD8+ T-cells: elevated levels of granzyme-B, perforin, human leukocyte antigen - DR isotype (HLA-DR), and TIGIT causing exhaustion of CD8+ cells.

Management of COVID-19 Infections

Unfortunately, no specific antiviral treatment is available and so far there is no available vaccine [14-16]. The current and potential therapeutic interventions that are being used in the management of COVID-19 infections are illustrated in table 3 [4,6,11,14,17,18,25,47,133-135,152-154,185,217,221-268]. Combinations of 2 or more therapeutic modalities appear to be more successful than using single agents [6,11,18].

Drug Repurposing or Repositioning

Drug repurposing refers to identification then use of drugs that have already been approved or used for the treatment of other medical illnesses in an attempt to shorten the time and reduce the costs of discovering and manufacturing new drugs [233]. Examples of existing drugs with therapeutic potential for COVID-19 that have been repurposed: (1) the antimalarial drug hydroxychloroquine; (2) various antiviral drugs such as: ribavirin (hepatitis C and respiratory syncytial virus), lopinavir and ritonavir human immunodeficiency virus (HIV), Arbidol (influenza viruses), remdesivir (Ebola virus), galidesivir (hepatitis C, Ebola and Marburg viruses), darunavir and favipiravir (HIV), and interferons (hepatitis C virus); (3) baricitinib (janus kinase inhibitor for rheumatoid arthritis); and (4) nitazoxanide for helminthic and protozoal infections [257-259]. However, more details are shown in table 3 [4,6,11,14,17,18,25,47,133-135,152-154,185,217,221-256].

Chloroquine and Hydroxychloroquine: Chloroquine and hydroxychloroquine; which are commonly used for the treatment of malaria, collagen vascular disorders and skin diseases; have been used in treating COVID-19 infection. They have the following actions of effects: (1) immunomodulatory effects through inhibition of cytokine production, autophagy, and lysosomal activity in host cells; (2) inhibition of proteolytic processing and endosomal acidification; (3) antiviral effects including impairment of viral replication, interference with posttranslational modification of viral proteins, and inhibition of binding of viral particles to cellular receptors; and (4) blocking virus-cell fusion and interference with glycosylation of SARS-CoV and ACE2 cellular receptors [225,228,232].

Azithromycin and Melatonin: Azithromycin is a macrolide antibiotic that has several actions including: (1) antimicrobial activity against Gram positive and Gram negative bacteria as well as atypical pathogens; (2) anti-inflammatory activity as it has been shown to reduce the blood levels of proinflammatory cytokines and chemokines; (3) immunomodulatory actions; and (4) antiviral activity as it has been shown to have in vitro activity against Zika and Ebola viruses [44,260,261]. In patients with COVID-19 infection, several studies have shown efficacy of azithromycin particularly when given in combination with chloroquine or hydroxychloroquine. However, some studies reported increased incidence of prolongation of QT interval, arrhythmias and death in patients receiving the combined therapy. So, cardiac toxicity limits the utilization of an effective combination therapy for the treatment of COVID-19 infections [261-268]. Melatonin; N-acetyl-5-methoxy tryptamine; is commonly used in the treatment of sleep disorders, delirium, respiratory diseases and viral infections. Melatonin has anti-inflammatory and antioxidant properties. It is protective against viral infections and could be beneficial in COVID-19 [269].

Use of Convalescent Serum or Plasma

The collection of blood from patients who have recovered from a contagious disease to treat other patients suffering from the same disease or to protect healthy individuals from acquiring the disease, by providing passive antibody treatment, has been practiced since the 1890s [154,235]. Convalescent serum or plasma is indicated as prophylaxis for individuals at high risk of developing disease including: individuals with comorbid medical conditions, health care providers, and individuals exposed to confirmed cases of COVID-19. However, therapeutic use; or the administration of convalescent plasma to patients with COVID-19 infection; should take into consideration the fact that passive antibodies are most effective when administered at an early stage of the disease or shortly after the onset of symptoms [235,238]. One possible explanation for the efficacy of convalescent plasma is that the antibodies obtained from the convalescent plasma might suppress viremia [236].

Several studies and 2 meta-analyses have shown that the effectiveness of convalescent serum or plasma and hyperimmune immunoglobulins in the treatment of a number of viral infections, and their associated ARDS complications, such as: (1) Ebola virus; (2) influenza A (H1N1) pandemic in 2009; (3) SARS; and (4) Spanish influenza pneumonia (H5N1) [236-243]. In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by the WHO as an empirical treatment during the outbreak [236,243]. Also, a protocol for the

use of convalescent plasma in the treatment of MERS-CoV was established in Saudi Arabia in the year 2015 [236,270,271]. However; the use of convalescent serum or plasma has been shown to have the following adverse effects or drawbacks: (1) antibodies in the plasma can overstimulate the immune system of the recipient and cause CRS which is potentially fatal; (2) the concentration of antibodies in the blood is usually low and consequently large volumes of plasma are required to treat these critically ill patients; (3) transfusion-related lung injury; (4) transmission of other infectious agents from the donors; (5) reactions to serum constituents such as serum sickness; and (6) the theoretical risk of antibody-dependent enhancement of COVID-19 infection [154,235].

Very few studies on the use of convalescent plasma in the treatment of COVID-19 have been published [154,256,237]. In one study, plasma was collected from the blood of patients who had recovered from COVID-19 and it was administered IV to 10 critically ill patients. The results of the study showed the following: symptoms improved within 24 hours, improvement in oxygen saturation in the blood, reduction in inflammation, and reduction in viral load [154]. The second study was an uncontrolled case series from Shenzhen in China. The authors reported 5 critically ill patients with COVID-19 related ARDS who received convalescent plasma that had been obtained from other patients recovering from COVID-19 infection. The following results were obtained: fever resolved in 4 patients, viral load decreased then became negative within 12 days of plasma infusion, 3 patients were weaned from mechanical ventilation, and out of the 5 patients treated 3 were discharged and 2 remained in stable condition in the hospital [237,256].

Table 3: Current and potential therapeutic interventions in COVID-19.

1- **Symptomatic treatment, supportive care, and treatment of complication:**
   a. Oxygen supplementation: high flow oxygen may be required.
   b. Non-invasive ventilation.
   c. Endotracheal intubation and mechanical ventilation.
   d. Fluid and electrolyte replacement.
   e. Management of septic shock and organ dysfunction.
   f. Treatment of secondary bacterial infection.
2- **Drug repositioning or repurposing:**
   a- Antiinflammatory drugs:
      (1) Chloroquine and hydroxychloroquine: used in the treatment of: malaria, rheumatoid arthritis (RA), and systemic lupus erythromatosus..
      (2) Corticosteroids and non-steroidal anti-inflammatory drugs.
      (3) Melatonin.
      (4) Tocilizumab: interleukin (IL)-6 inhibitor used in the treatment of cytokine release syndrome.
      (5) Sarilumab: IL-6 receptor agonist approved for the treatment of RA.
      (6) Inhibitors or blockers of: Janus kinase (JAK), IL-1, IL-17, and tumor necrosis factor
   b- Antiviral agents:
      (1) Ribavirin: approved for treatment of hepatitis C virus (HCV) and respiratory syncytial virus infections.
      (2) Interferons (α and β): approved for treatment of HCV, hepatitis B virus, and chronic myeloproliferative neoplasms.
      (3) Favipiravir: RNA polymerase inhibitor used for treatment of Ebola and Influenza viruses.
      (4) Remdesivir: RNA polymerase inhibitor and novel nucleoside analogue prodrug developed for treatment of Ebola and SARS viruses.
      (5) Oseltamivir: neuraminidase inhibitor that has been approved for treatment of influenza.
      (6) Other antiviral drugs: lopinavir, ritonavir, and darunavir.
   c- Other medications:
      (1) Arbidol: inhibition of membrane fusion to the viral envelope [inhibits S protein and angiotensin converting enzyme (ACE2) membrane fusion.
      (2) Camostat mesylate: used for the treatment of chronic pancreatitis and targets TMPRSS2 protease.
      (3) Teicoplanin: glycopeptide antibiotic used in the treatment of staphylococcal infections.
      (4) ACE inhibitors and neutralizing antibodies that target ACE receptors.
      (5) Ivermectin: antiparasitic agent with broad-spectrum antiviral activity in vitro.
      (6) Enfuvirtide: peptide that inhibits membrane fusion used in the treatment of human immunodeficiency virus..
3- **Chinese traditional medicine.**
4- **Convalescent serum or plasma containing viral antibodies.**
5- **Auxiliary blood purification therapy.**
6- **Cellular therapies:**
   a- Mesenchymal stem cells and their secretomes.
   b- Other immune cells: granulocytes, mononuclear cells, dendritic cells, and natural killer cells.
7- **Precision medicine (not yet available):** therapies that target viral replication and therapies directed against targets within the virus genome
8- **Other lines of management:**
   a- Infection control measures.
   b- Vaccination
   c- Psychological support for patients and their families.

Removal of Cytokines from the Circulation

Inflammatory cytokines can be removed from the circulation using the following techniques: (1) direct hemoperfusion using a neutro-macroporous sorbent; (2) plasma adsorption on a resin after plasma separation from whole blood; (3) continuous renal replacement therapy (CRRT) with hollow fiber-filters having adsorptive properties; and (4) high-dose CRRT with medium or high cut-off membranes [244,272]. However, CRRT is the predominant form of renal replacement therapy in patients with AKI and sepsis admitted to the ICU [245]. In patients with septic shock, the application of blood purification therapies to remove cytokines and endotoxins from the circulation using high volume continuous hemofiltration or adsorbent therapy using advanced sorbent technology looks a tempting idea but results of the scarce studies performed so far were rather disappointing [246].

In patients with SARS-CoV associated ARDS and H7N9 influenza infection, cytokine removal using plasma exchange module in artificial-liver blood purification or continuous veno-venous hemofiltration module had shown remarkable efficacy. Thereafter, an expert consensus report was released and it recommended the use of artificial-liver blood purification therapy in critically-ill COVID-19 patients in the following situations: (1) plasma concentration of blood inflammatory cytokines, such as IL-6, ≥5 times above the upper limit of normal or a daily rise of > 1 fold; (2) rapid daily progression of lung involvement ≥ 10% based on CXR or CT scan of lungs; and (3) medical comorbidities requiring artificial blood purification therapy [247].

Extracoporeal therapies have been proposed to remove cytokines in patients with septic shock and they are potentially beneficial in critically ill patients with COVID-19 as cytokine removal could prevent CRS-induced organ damage [244,272]. In the United States of America (USA), the FDA has already approved the use of Terumo BCT's and Cytosorbent's blood filtering devices for use in patients with severe COVID-19 infections [273]. However, hemoperfusion should be used for at least 2 hours on 3 consecutive days and anticoagulation with heparin or citrate should also be used during the procedure to prevent premature clotting of the circuit [272].

In patients with COVID-19, pneumonia is mediated by IL-6, cytokine storm or CRS and it is an important cause of death [248]. Tocilizumab, a recombinant humanized monoclonal antibody which effectively blocks IL-6 receptor, is likely to become an effective therapeutic modality in treating patients with COVID-19 infections [248]. Tocilizumab has been used in the treatment of: (1) CRS associated with chimeric antigen receptor (CAR)-T cell therapy; and (2) rheumatoid arthritis [248-251]. In a murine model, fedratinib has been found to: suppress the expression of IL-17, profoundly suppress the expression of IL-23, and suppress the function of GM-CSF but effects on IL-21 expression were rather marginal. So, fedratinib could suppress the production of several Th17 signature cytokines that are associated with poor outcome in patients with COVID-19 infections [252].

Host-Directed Therapies (HDTs) for Viral and Bacterial Infections

HDT is an emerging approach or strategy in the field of anti-infective treatments aimed at: (1) interference with host cell factors that are required by the pathogen for replication or persistence by targeting disease-causing virulence factors; (2) augmentation of the cellular protective immune responses against pathogens; (3) modulation or reduction of exacerbated inflammation; and (4) activation of innate and adaptive protective immune responses and balancing immune reactivity at the sites of pathology [255,274]. Thus, host-directed therapeutic strategies are becoming viable adjuncts to standard antimicrobial therapies with the ultimate goal of reducing end-organ damage as well as morbidity and mortality [274]. Also, discovery and characterization of cellular factors or pathways that are critical for pathogen life cycle in a host hold great promise for revealing new anti-infective therapeutic strategies [275].

Examples of infectious diseases that can be targeted by HDT: (1) pulmonary and extrapulmonary tuberculosis; (2) sepsis due to: Gram positive and Gram negative bacteriae and fungal organisms; and (3) viral infections such as hepatitis B, C, and D viruses in addition to HIV, Ebola virus, Dengue virus, and MERS-CoV [255,274,276]. In viral infections, targeting the host cell factors and pathways that are required by a given virus for productive replication and spread offers the opportunity for broad-spectrum antiviral drugs [255].

Advantages of HDTs include: (1) safety, low cost, and being readily available for use; (2) prevention or reduction of the development of antimicrobial drug resistance; and (3) treatment of infectious diseases with epidemic potential that are associated with high mortality such as COVID-19 [274]. It is essential to target host factors for the following reasons: (1) the viral genomes, particularly that of SARS-CoV-2 virus, have very high mutation rate; (2) targeting host factors may

have a broad antiviral spectrum; and (3) both COVID-19 and SARS have cytokine storms resulting in pneumonia, ARDS, and death [275]. Examples of HDTs that can be utilized in the treatment of COVID-19 include: (1) cellular therapies such as autologous MSCs; (2) zinc and nutritional supplements; and (3) commonly used drugs such as metformin, cyclosporine-A, IFN-beta 1b, and ribavirin [230,274].

Potential Targets and Drug Candidates for COVID-19

The potential target proteins and examples of their drug candidates can be divided into the following categories: (1) drug targets that prevent the virus RNA synthesis and replication such as lopinavir, remdesivir, and favipiravir; (2) drug targets that inhibit viral structural proteins such as posaconazole and itraconazole; (3) targets that inhibit virulence factors such as tetracycline and streptomycin; and (4) drug targets that block hose specific receptors or enzymes such as losartan, and ergotamine [259]. More details on target proteins and their drug candidates are shown in table 4 [257,259,276].

The main protease M^{pro} of SARS-CoV-2 is the key enzyme that plays a pivotal role in mediating viral replication and transcription, thus it can serve as the primary drug target [277,278]. However, the following categories of compounds have been found to strongly bind to SARS-CoV-2 as they have high affinity for it: (1) several natural compounds such as δ-viniferin, myricitrin, 15-oxalate, and hesperidin; (2) various drugs that have antiviral actions including ritonavir, oseltamivir, remdesivir, ribavirin, and favipiravir; and (3) two synthetic compounds labelled as 11a and 11b [277-279]. Studies have shown that: (1) the peptide KRSFIEDLLFNKV is well conserved across coronaviruses and this may imply that they have common zoonotic origins; (2) coronavirus N7-MTase may be an attractive target for developing new antiviral agents; and (3) after searching public datasets using various genetic and genomic techniques, 36 drugs were initially described as potentially active against COVID-19, but finally only didanosine proved to have actual antiviral activity [280-282].

Clinical Trials on COVID-19

In addition to the unavailability of a specific antiviral treatment and a vaccine for COVID-19, the speed of normal drug development pathway, which takes many years, is unacceptable in the context of the current global epidemic [14-16]. Worldwide, more than 1100 clinical studies have been registered; more than 500 of them are randomized controlled trials; with the intention of discovering drugs that effectively treat COVID-19 infections. These clinical trials are exploring new preventive strategies and therapeutic interventions including: vaccine development, use of convalescent plasma, IFN-based therapies, small molecule drugs, cell-based therapies, and monoclonal antibodies [14,16,283].

Depending on their targets, the ongoing clinical trials on potential antiviral therapies are divided into 2 main categories: (1) drugs acting on the coronavirus directly either by inhibiting crucial viral enzymes responsible for genome replication or by blocking viral entry to human cells; and (2) therapies designed to modulate the human immune system either by boosting the immune response or by inhibiting the inflammatory processes that cause lung injury [284]. Depending on their aims, the ongoing trials are classified into 4 main types: prophylaxis, treatment of outpatients with mild COVID-19, treatment of hospitalized patients with moderate COVID-19, and treatment of critically ill patients with COVID-19 [16]. Based on the time-line, the ongoing clinical trials are divided into 2 main types: (1) long-term trials on SARS-CoV-2 genome-based specific vaccines and therapeutic antibodies and these require thorough testing for their safety; and (2) short-term trials using repurposed drugs that have been tested for safety and these constitute a practical approach or a rapid response measure to the rapidly emerging pandemic [284]. Finally clinical trials are mapped according to specific characteristics including: geographic location, category of patients included, and interventions made [283].

The rapid development and launching of clinical trials is rather impressive, but presents challenges including the potential of duplication and competition [12,16]. However, COVID-19 clinical trials should be adequately powered so as to generate evidence [285]. Large, well-documented clinical trials are urgently required to support development of guidelines on prevention as well as clinical management. Therefore, the WHO should have a central role in reviewing the evidence generated by these trials and in implementing management guidelines [285].

Vaccination

Vaccines, which are designed to boost the natural immune response against the invading pathogen, represent the most effective means to save lives, preserve good health, and maintain high quality of life [286-288]. Vaccines can be developed from live-attenuated organisms, protein subunits, or killed organisms [289]. Development of a safe and effective vaccine

with adequate delivery systems is an imperative need to obtain the desired humoral and cellular immunity against infectious diseases [288,289].

Vaccination strategies include the use of: inactivated virus, DNA plasmids, viral vectors, nanoparticles, virus-like particles, and recombinant protein subunits [154]. Additionally, subunit vaccines are introduced on the basis of: full-length spike protein, receptor-binding domain (RBD), non-RBD protein fragments, and non-structural proteins [290]. General indication for vaccination include: elderly individuals, immunocompromised hosts, and exposed individuals including health care workers [291]. The recent advances in recombinant DNA technology have accelerated the speed at which vaccines against emerging infections can be designed and produced. By combining emerging technology methods and bioengineering advances in vaccine delivery strategies, it may become possible to rapidly produce and globally distribute vaccines against novel human pathogens to decrease the burden of viral infectious diseases [288,292,293].

Currently, in the absence of an effective vaccine against COVID-19, efforts to develop effective vaccines are ongoing [293]. However, it is crucial to develop vaccines to: (1) control the COVID-19 pandemic; (2) eliminate the spread of the virus infection; and (3) ultimately prevent its future recurrence [154,257]. Since the SARS-CoV-2 virus shares significant sequence homology with 2 other lethal coronaviruses; SARS, and MERS; the vaccines identified for these 2 viruses could potentially facilitate the design of anti-SARS-CoV-2 vaccines. Also, compared to other vaccine types; such as inactivated virus or viral-vectored vaccines; SARS and MERS subunit vaccines are much safer and do not cause obvious side effects [257,290,293,294].

Structure and epitope-based vaccine design have become promising strategies to improve the efficacy of subunit vaccines [290]. Moderna Incorporation released its first patch of messenger RNA (mRNA)-1273 against SARS-CoV-2 in February 2020 and the vaccine is ready for phase I study in the USA [257,286]. Clinically translatable microneedle arrays (MNAs)-SARS-CoV-2 subunit vaccines were produced within 4 weeks of the identification of SARS-CoV-2 S1 sequence and these MNA-delivered SARS-CoV-2 S1 subunit vaccines elicited potent antigen-specific antibody responses 2 weeks after vaccination [292]. A set of B-cell and T-cell epitopes derived from the spikes and nucleocapsid proteins that map identically to SARS-CoV-2 proteins have been identified and this will help to guide the experimental efforts towards development of vaccines against SARS-CoV-2 virus [294].

The traditional vaccine for tuberculosis bacille Calmette-Guerin (BCG) has recently been suggested as a possible agent to prevent COVID-19 [253,254,295,296]. This suggestion was based on the following data: (1) recent epidemiological studies have shown that 7 out of the 8 countries low mortality rates related to COVID-19 have adopted mandatory BCG vaccination, while mortality rates due to COVID-19 were higher in countries which discontinued BCG vaccination more than 20 years ago; (2) other epidemiological observations showing that BCG vaccination can decrease susceptibility to respiratory tract infections by boosting immunity of the host; (3) in animal studies, BCG vaccine has been found to offer protection against both RNA and DNA viruses via induction of innate immune memory and heterogeneous lymphocyte activation; and (4) a recent study on health human volunteers has shown that BCG vaccination could reduce viremia in response to the live-attenuated vaccine of yellow fever [253,254,296-299]. Unfortunately, several recent articles showing epidemiological protection have been retrieved. So far, there is no solid evidence to recommend BCG vaccination for protection against COVID-19 [300]. Studies are in progress to determine whether BCG vaccine could provide protection against COVID-19 [295]. Two randomized controlled trial are currently testing the role of BCG vaccination in the prevention of COVID-19 in Australia and the Netherlands [296].

Table 4: Drug Candidates for COVID-19 and their Target Proteins or Receptors.

Target Protein(s) or Receptor(s)	Drug Candidate(s)
Papain-like proteinase (**PLpro**)	Lopinavir; Ribavirin
Coronavirus main protease [3C-like main protease; **3CLpro**]	Lopinavir
RNA-dependent RNA polymerase (**RdRp**)	Remdesivir; Favipiravir
Helicase	Saquinavir
Transmembrane protease serine 2 (**TMPRSS2**)	Camostat mesylate
Viral spike glycoprotein/ Angiotensin converting enzyme-2 (**S protein/ACE2**)	Arbidol
Endosome/ACE2	Chloroquine; Hydroxycholoquine
Angiotensin AT2 receptor (**AT2**)	L-163491
Janus kinase (JAK)	Bavicitinib

Prevention and Control of COVID-19 Pandemic

The following preventive measures have been implements: (1) hand hygiene and hand washing with disinfectant soap; (2) use of the surgical face mask or the N95 respiratory mask; (3) stratified quarantine for patients, contacts, and health workers either at home or in hospital; (4) health care providers should wear fitted isolation gowns; and (5) keeping distance of 3 feet between people [154,301,302]. Non-pharmacological public health interventions to control outbreaks of infectious diseases include: isolation of infected cases, quarantine, and community containment by social distancing, use of masks and gloves, and complete locking of suburbs, cities, and districts [303].

The 2 main strategies that have emerged since COVID-19 became a pandemic are strict application of infection control measures including quarantine and allowing the development of herd immunity in the population [303-307]. Quarantine is lockdown or restriction of movement of individuals who are presumed to be exposed to a contagious disease but are not ill either because they are not infected or because they are still in the incubation period [303,304]. Herd immunity refers to allowing the virus to spread in the population so as to increase the population herd immunity but to protect individuals who are most vulnerable to the infection such as elderly persons and patients with medical comorbidities [305].

The serial interval of COVID-19 is short and close to or shorter than its incubation period which suggests that a substantial proportion of secondary transmission may occur prior to the onset of the illness. Additionally, a short serial interval makes it difficult to trace contacts due to the rapid turnover of case generation [308]. The estimated number of people who could potentially die from COVID-19 once the population reaches the critical or minimum level of population immunity may be difficult to accept as it is likely to be exceptionally high [305]. Early implementation of quarantine and combining it with other public health measures is important to ensure the effectiveness of infection control programs [306]. However, rapid control of the COVID-19 pandemic can be achieved by fulfilling the following requirements: (1) rapid detection of the virus, tracing its origins, and tracking the new genetic mutations; (2) limitation of the virus spread by implementation of specific control measures; (3) exchange of data across disciplines and in between countries; and (4) use of technical advances not only in the diagnostics but also in the rapid development of effective drugs and vaccines [37,38,42,309].

Various Approaches Used in the Management of COVID-19

It is important to adopt a multidisciplinary therapeutic approach that takes into consideration the specific condition as well as the circumstances of each patient [310-312]. However, a precision medicine approach is urgently needed to diagnose the disease at an early stage and to control the spread of the infection [302]. Hopefully, better understanding of the pathogenic pathways and accurate phenotype classification in addition to definition of disease biomarkers and other advanced diagnostic tools will ultimately lead to more personalized therapeutic options in the use of pharmacological agents as well as biological therapies in the treatment of COVID-19 pandemic [313].

Medical applications of artificial intelligence methods, particularly deep learning, have shown excellent outcomes [314]. In fighting COVID-19 pandemic, artificial intelligence and deep learning have shown promising results once applied to: drug repositioning or repurposing, drug discovery and development, vaccine development and manufacture, and diagnostic radiological techniques used in COVID-19 screening [314-316].

MSCs and Their Future Role in COVID-19

General Overview of MSCs

Stem cells are a subset of biological cells in the human body that are capable of self-renewal, differentiation, tissue repair, and division into different cell lineages [317-320]. Based on their potency and origin, stem cells are divided into: either (1) embryonic and adult stem cells; or (2) unipotent, oligopotent, totipotent, multipotent, and pluripotent stem cells [317,318,320,321]. Multipotent or adult stem cells include MSCs, while pluripotent stem cells include embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [317-322].

MSCs are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of not only self-renewal but also differentiation into multiple lineages and various cell types [19,20,322-327]. MSCs were first described by Alexander Fridenstein in the 1960s and they can be isolated from several sources including BM, PB, adipose tissue (AT), UC blood (UCB), amniotic fluid, placenta, and dental pulp as shown in table 5 [19,20,322-327]. Although the BM is the main source of MSCs, MSCs constitute only a small fraction of the total number of cells populating the BM [19,323-325].

MSCs have the following distinguishing features: (1) differentiation into osteoblasts, adipocytes, and chondrocytes; (2) adherence to the plastic vessel under optimal culture conditions; and (3) having characteristic surface markers on flow cytometry as they are characteristically positive for: CD 105, CD 73, and CD 90 and characteristically negative for the following surface markers: CD 45, CD 34, CD11b, CD14, CD19, CD79a, and HLA-DR. However, certain types of MSCs can occasionally show positivity or negativity for specific surface markers as shown in table 6 [19,20,322,324,325,327-333]. Several studies have shown that MSCs can differentiate into other cell types such as cardiomyocytes, myocytes, and neurons and that MSCs derived from BM, AT, and other sources do express CD 34 surface marker under certain circumstances [323,324,334-337]. Additionally, MSCs can be seen in abundant numbers in the circulation under the following conditions: stem cell mobilization with growth factors, stroke, hypoxia, tissue injuries, as well as inflammatory conditions [323,338-343]. Unfortunately, little is known about the molecular basis underlying the stemness of MSCs and it is still unclear whether the recently discovered transcriptional factors and genes regulate stemness or only differentiation of MSCs [326].

MSCs have immunomodulatory and immunosuppressive properties as well as antimicrobial actions that enable them to have several therapeutic and clinical applications including: HSCT, autoimmune disorders, tissue repair and regenerative medicine, neurological diseases, bone and cartilage disorders, in addition to the treatment of several infections and their complications including ARDS as shown in table 7 [19,20,326,327,344-348].

MSCs from UCB

MSCs derived from UCB are considered the optimal source compared to other sources of MSCs as UCB-MSCs have the following advantages: (1) they are easily accessible and can be obtained without using invasive procedures; (2) isolation of these stem cells does not carry any risk to the donor; (3) high concentrations of stem cells with high proliferative capacity can be obtained; (4) efficient expansion in the laboratory; (5) they are scalable which is an important aspect taking into consideration the large numbers of coronavirus victims; (6) their gene expression profile is similar to that of ESCs without having ethical concerns surrounding their use; (7) allogeneic MSCs cause no rejection; and (8) they have the following immunomodulatory and immunosuppressive properties that may be beneficial in COVID-19 pneumonia: (a) improvement of oxygenation, (b) amelioration of lung injury, (c) reduction of pathogen load, (d) amelioration of the levels of inflammatory markers and modulation of the signals of inflammatory pathways, (e) stimulation of tissue regeneration and angiogenesis, and (f) recruitment of endogenous stem cells [22-25]. The IV route of administration seems to be the most desirable for MSC infusion or administration [25]. Human UC-MSCs can be obtained from different compartments of the UC and can subsequently be processed by different techniques [22].

Antimicrobial Properties of MSCs

MSCs have been shown to exhibit the following antimicrobial properties: (1) detection and elimination of the invading pathogen by enhancing bacterial clearance, (2) activation of the host immune response by induction of proinflammatory gradients or responses, and (3) secretion of antimicrobial peptides, molecules, and proteins such as IL-17, and indoleamine 2,3 dioxygenase [20,21,25]. By secretion of paracrine factors, microvesicles and transfer of mitochondria, MSCs can exert

the following beneficial effects in patients with ARDS: (1) reduction of pulmonary edema, (2) resolution or healing of lung injury, (3) antimicrobial properties, and (4) upregulation of monocyte/macrophage phagocytosis [21,349]. In a phase-I clinical trial, Jennifer Wilson et al showed safety of allogeneic BM-MSCs administered to patients with ARDS [21,350]. In a mouse model of influenza ALI, UC-MSCs were effective in restoring alveolar fluid clearance and protein permeability of avian influenza A (H5N1)-infected human cells but they had only modest improvement on survival of H5N1 infected mice [24]. Studies have shown that: (1) MSCs are susceptible to infection by members of the herpes group of viruses but not to hepatitis B virus and (2) human MSCs are permissive to H5N1 and infection of MSCs by this virus can adversely affect their immunomodulatory function but they can still retain their ability to enhance fluid clearance and ameliorate lung injury [21,351,352]. MSCs have been used successfully in the treatment of several infections such as: multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis, Chagas disease, viral infections including HIV, in addition to sepsis and ARDS. Although more success has been achieved in preclinical studies using animal models than in human clinical trials, particularly in septic shock and Chagas disease, more progress has recently been achieved in MDR and XDR tuberculosis after using specific sources and certain doses of MSCs [19,21,347,350,351,353-368].

Effects of MSCs on Lungs

MSCs have the following effects on the lungs: (1) immunomodulatory effects; (2) protection of alveolar epithelial cells; (3) restoration of pulmonary microenvironment; (4) prevention of pulmonary fibrosis; (5) reversal of pulmonary dysfunction and control of COVID-19 pneumonia; (6) prevention of cytokine release by the immune system and promotion of endogenous repair by means of the reparative properties of MSCs; and (7) after IV administration, a significant proportion of MSCs home or accumulate in the lungs so a limitation can become an advantage in case of ALI or ARDS

Table 5: Sources of mesenchymal stem cells.

1- Bone marrow
2- Peripheral blood
3- Saphenous veins
4- Umbilical cord blood: Wharton's jelly
5- Placenta: chorionic villi of placenta
6- Amniotic fluid
7- Menstrual blood
8- Fallopian tubes and cervical tissue
9- Breast milk
10- Adipose tissues: fat
11- Dental pulp, periodontal ligaments, exfoliated deciduous teeth
12- Salivary glands
13- Palatal tonsils
14- Skeletal muscle tissues
15- Dermal tissues
16- Liver tissues: fetal liver
17- Lung tissues and alveolar epithelium
18- Synovial membrane and fluid
19- Parathyroid glands

Table 6: Surface markers of Mesenchymal Stem Cells on Flow cytometry.

	Positive	Negative
Characteristic surface markers	CD105 CD73 CD90 MHC-I (low expression)	CD 45 CD 34 CD 14 CD 11b CD 19 CD 79a HLA-DR MHC-II
Other surface markers that can be expressed	CD117 CD33 CD166 CD49b CD29 CD71 CD44 CD164 CD106 CD271 CD9 HLA-class I CD10 Stro-1 CD13 SSEA-4 CD28 ITGA-11	CD 31 CD 33 CD 133
CD34 is a surface marker that should be highlighted separately	Positive in short-term cultures	Negative in long-term cultures

MSCs: Mesenchymal Stem Cells; HLA: Human Leukocyte Antigen; MHC: Major Histocompatibility Complex

[29,369]. The following are advantages of MSCs over other stem cells: (1) they are multipotent with high proliferation rate; (2) they are easily accessible and can be isolated from various tissues using no or minimally invasive procedures; (3) they can be easily expanded to clinical volume in a suitable period of time; (4) their use is free of ethical concerns that limit the use of ESCs; (5) they can be stored for repetitive therapeutic usage; (6) safety as clinical trials on the use of MSCs have not shown adverse reactions to allogeneic MSCs; and (7) clinical efficacy has been documented in several clinical trials [29]. MSCs have been found to modulate the functions of the following immune cells: T-cells, B-cells, NKCs, DCs, cytotoxic T-cells, macrophages, and neutrophils [370].

Recently, countries such as China, USA, Jordan, and Iran have begun using cellular therapies in clinical trials for the treatment of COVID-19 infections with approximately 70 trials registered, 20 of them in China, and 17 completed. The vast majority of trials use MSCs derived from UCB with few trials using MSCs derived from other sources such as dental pulp and menstrual blood. Some trials are using: NKCs, ESCs, and products of MSCs such as exosomes. Few of these trials use the combination of MSCs and NKCs or ruxolitinib [25,29,371].

MSCs in Sepsis

MSC therapy has been shown to exert the following effects in animal models of sepsis: (1) increased survival, (2) reduction of inflammation, (3) enhancement of bacterial clearance by increasing phagocytic activity of blood monocytes, (4) improvement in organ function such as renal function, and (5) regulation of immune response of the host to sepsis by: reducing inflammatory cytokines in blood and lungs, decreasing cell infiltration in lung alveoli, and prevention of apoptosis in the kidneys in response to endotoxemia [372-379].

Mechanisms of protective effects of MSCs on sepsis include: (1) involvement of a range of activities affecting multiple biological networks and signaling pathways that play critical role, (2) BM stromal cells have been found to attenuate sepsis via prostaglandin E2-dependent reprogramming of host macrophages to enhance their IL-10 production, and (3) MSCs are capable of increasing numbers of macrophages in the circulation and inducing immunomodulatory capabilities in macrophages [372,380,381]. Thus, neutrophils are crucial in the beneficial role of MSCs therapy in polymicrobial sepsis [377].

Extracellular Vesicles (ECVs) of MSCs

MSCs are ideal candidates in the treatment of sepsis, in which inflammation plays a critical role, due to their immunosuppressive and anti-inflammatory properties [382]. ECVs are partially responsible for the paracrine effects of MSCs. In addition, they are safer and have a lower immunogenicity than MSCs and these features make them an ideal

Table 7: Current and potential therapeutic indications of mesenchymal stem cells.

1. **Hematopoietic stem cell transplantation:** enhancement of engraftment, prevention and treatment of graft versus host disease (GVHD).
2. **Solid organ transplantation (SOT):** improvement of outcome of SOT by immunomodulation and induction of transplantation tolerance.
3. **Treatment of autoimmune diseases:**
   - a. Systemic lupus erythromatosus b- Rheumatoid arthritis c- Systemic sclerosis d- Ankylosing spondylitis
   - e- Multiple sclerosis f- Type 1 diabetes mellitus g- Ulcerative colitis h- Crohn's disease
   - i- Type II refractory celiac disease j- Autoimmune: myasthenia gravis, uveitis, neuromyelitis optica and hearing loss.
4. **Regenerative medicine and tissue repair:**
   - a- Myocardial ischemia b- Acute myocardial infarction c- Cardiac dysfunction d- Dilated cardiomyopathy
   - e- Chronic non-healing wounds f- Critical limb ischemia g- Peripheral vascular disease h- Ischemic stroke
   - i- Traumatic brain injury j- Spinal cord injuries k- Liver injury l- Radiation-induced lung fibrosis
   - m- Tissue repair: bone, cartilage, muscle, skin, myocardium, trachea, etc.
5. **Treatment of various infections:**
   - a- Bacterial infections including sepsis and its associated adult respiratory distress syndrome
   - b- Viral infections such as human immunodeficiency virus, hepatitis B and C viruses
   - a- Parasitic infections such as Chagas disease and malaria
   - b- Mycobacterial infections such as tuberculosis
6. **Other indications:**
   - a- Macular degeneration, corneal regeneration or reconstruction and corneal transplantation
   - b- Liver fibrosis, liver cirrhosis, end-stage liver disease and hepatic failure
   - c- Bones and joints: osteogenesis imperfecta, osteoarthritis, osteoporosis, osteonecrosis, meniscus injury.
   - d- Cancer gene therapy and anti-cancer cellular therapy e.g. breast and lung cancer
   - e- Aging frailty f- Amyotrophic lateral sclerosis g- Parkinsonism h- Idiopathic pulmonary fibrosis
   - i- Chronic obstructive airway disease j- Kidney disease

alternative to whole cell therapy provided by MSCs in the treatment of sepsis [382]. In a variety of animal models of human lung diseases; such as inflammatory lung disease, ALI, hemorrhagic shock and viral infections; and compared to MSCs, ECVs derived from MSCs have been shown to have: (1) superior safety profile, (2) storage ability without loss of function, (3) suppression of proinflammatory processes, (4) reduction of oxidative stress and fibrosis, (5) attenuation of virus-induced lung injury, and (6) enhancement of tissue repair [383-386]. Compared to MSCs, ECVs derived from MSCs have the same anti-inflammatory and immunomodulatory effects and several advantages such as lower immunogenicity and higher safety profiles. So, MSC-ECVs can be used as a novel and an alternative therapeutic modality to whole cell therapy [387,388].

Therapeutic effects of MSC-ECVs in preclinical animal models include: reduction of neutrophils in BAL, reduction in inflammatory cytokines, decrease in fibrosis, reduction in pulmonary artery pressure and right ventricular hypertrophy, reduction in lung injury and edema, improvement in lung function, reduction in alveolar cell death, enhancement of alveolization and agiogenesis, in addition to improvement in survival [30]. So far, only few groups of scientists have studied the therapeutic effects of MSC-ECVs in ALI which is an attractive area of research [389].

Induction of secretory modifications in MSCs can be achieved by: hypoxia, proinflammatory stimuli, tri-dimensional growth, and microparticle engineering [28]. The clinical outcomes of MSC-based therapies including the secretomes of BM-MSCs are affected by: the use of immunosuppressive medications, and the presence of endotoxemia [390]. MSCs derived from ESCs confer less immunomodulatory effects than can be improved using conditioning with hypoxia, but higher production of inflammatory molecules such as TNF-α than BM-derived MSCs [391]. Apoptotic bodies are released from the plasma membranes as blebs when cells undergo apoptosis [392].

Therapeutic benefits of MSC-conditioned media (CM) in preclinical animal models include: reduction of neutrophils and other inflammatory cells in BAL, decreased proinflammatory cytokines, reduction in airway inflammation, decrease in lung fibrosis, reduction in pulmonary artery pressure and right ventricular hypertrophy, and increased survival [30]. The administration of MSC-CM and ECVs has been shown to be as effective as transplantation of MSCs in the attenuation of acute and chronic inflammatory lung diseases and thus MSC-CM/MSC-ECVs may become an alternative therapeutic modality [27,389]. Unfortunately, the potential use of of MSC-CM in clinical trials is limited more than the use of stem cells due to the lack of standardization of the use of CM [389].

Exosomes of MSCs

Exosomes are ECVs that contain proteins, mRNAs and DNAs and they are produced from body fluids and by different cell types including MSCs [393-395]. Exosomes derived from MSCs exhibit functions similar those of MSCs but with low immunogenicity and no tumor formation [393]. Exosomes derived from UCB-MSCs have been more frequently used in regenerative medicine and in the treatment of various diseases at experimental stage compared to exosomes derived from other sources of MSCs [393,394]. Exosomes derived from MSCs have a content that includes: cytokines, growth factors, signaling lipids, mRNAs, and regulatory micro-RNAs (miRNAs) [395]. Exosomes and microvesicles can influence tissue responses to: injury, infection, and disease [395]. Genetically modified mouse MSCs expressing non-structural protein of HCV can induce immune responses and thus can be used in the development of effective vaccines against HCV infection [396]. Exosomes derived from UCB-MSCs can inhibit viral infections such as HCV infection. Thus, exosomes from UCB-MSCs can be used for future development of antiviral agents [397].

Exosomes are efficient against reperfusion injury as they can prevent it. Also, exosomes can act as therapeutic agents or pharmacological drugs thus they represent a novel, safe, and refined modality of MSC therapy [398]. Exosomes derived from AT-MSCs can transfer miRNA-125a to endothelial cells and promote angiogenesis by inhibiting Delta-like 4. Thus exosomes derived from AT-MSCs, by acting as proangiogenic factor, might become a promising candidate for tissue repair and regeneration [399].

Exosomes represent a new exciting avenue to explore viral pathology as they play roles in both transient and latent viral infections [400]. Viruses utilize many mechanisms, including insertion of their components in exosomes, by which they evade and subvert the immune system of the host to ensure their survival and persistence [400]. Host-derived exosomes and the transport of pathogen-derived molecules by exosomes impact infections in various ways [401]. Exosomes play a key role in immune modulation and cell to cell communication and MSC-exosomes may deliver bioactive proteins, lipids, and nucleic acid cargo to the neighboring injured or diseased cells so as to induce functional changes in the recipient cells [392].

MSC-Secretome

MSCs secrete or release biologically active factors or substances, referred to as secretomes, that are made of: (1) ECVs including exosomes, microvesicles and apoptotic bodies, (2) soluble proteins including: cytokines, chemokines, and growth factors, (3) lipids, (4) nucleic acids, and (5) CM [26-28,30,392,402]. Advantages of secretome compared to MSCs or other interventions include: (1) secretome may bypass the side effects of MSC-based therapy such as differentiation of engrafted cells, so it is generally safer than MSCs; (2) secretome is immediately available for the use in the treatment of acute conditions and it can be readily used for emergency interventions; (3) secretome can be massively produced from commercially available cell lines avoiding invasive collection procedures; (4) secretome has technical advantages and can be manipulated and stored more easily than MSCs; and (5) the costs of MSC-secretome is probably lower than other therapeutic interventions such as ticilizumab [26-28].

Therapeutic actions or effects of MSC-secretome including those in lung diseases: (1) anti-inflammatory effects such as suppression of cytokine production in ALI; (2) regenerative and proliferative effects with enhancement of wound healing and tissue repair; (3) antimicrobial effects; (4) anti-oxidant effects or attenuation of oxidant-mediated lung injury; (5) immunomodulatory and immunosuppressive effects including attenuation of antigen presenting function of certain cells such as DCs; (6) proangiogenic properties and regulation of angiogenesis; (7) antifibrotic effects or suppression of collagen deposition in tissues such as lungs; and (8) other effects including antitumor effects and neuroprotective effects [26-28,30,392,402].

The therapeutic potential or efficacy of MSCs in several animal models of pulmonary disorders and in early clinical trials in ARDS might be attributed to their secretome. Thus, MSC-derived secretome might become an appropriate therapeutic modality for the treatment of aggressive pulmonary disorders because of its biological and logistical advantages over live cell therapy [30]. Secretome-derived products could significantly improve multiple biomarkers of pathophysiology in many animal models of different diseases. Also, secretome-based approaches using CM or exosomes may present considerable potential advantages over living cells with respect to manufacturing, handling, storage, product shell-life, and the potential for immediate use in emergency situations [28]. MSC-secretome could offer a new therapeutic approach in treating COVID-19 pneumonia due to its broad pharmacological and therapeutic effects and in patients with ARDS, the effectiveness of MSC-secretome in preclinical conditions is clear both in vivo and in vitro [26].

After IV injection of MSC-secretome, the secretome remains highly stable in the peripheral circulation and it spreads into lung tissues to provide the following effects: immunomodulation, resolution of inflammation, restoration of capillary barrier function, and enhancement of bacterial clearance [26]. The biological rationale for using MSC-secretome is based on: (1) the vast majority of studies have demonstrated that the mechanisms underlying the therapeutic effects of MSCs were due to the secretion of soluble factors, (2) most preclinical studies have shown that engraftment rates of MSCs were < 5%, and (3) several studies have demonstrated that cell-free MSC-derived CM recapitulated the therapeutic effects of MSCs in ALI. Thus, MSC-secretome holds great promise as a controllable, manageable, and plausible therapeutic strategy and has recently received attention as a paradigm for cell-free tissue repair and regeneration [389,392]. MSC-secretome acts on several cytokines simultaneously and synergistically and if MSC-secretome can be formulated as a freeze-dried powder and administered as IV or by inhalation, it may represent a suitable approach for the treatment of COVID-19 pneumonia particularly in patients who are critically ill [26]. The beneficial effects of MSC-secretomes depend on their capacity to deliver genetic material and growth as well as modulatory factors to the target cells enabling the activation of anti-apoptotic and prosurvival pathways and ultimately resulting in enhancement of tissue repair and regeneration [27].

Homing of Transplanted or Infused MSCs

The therapeutic effect of MSC-based therapeutics relies on their ability to home or reach the sites of injury in the lungs [403-405]. Unfortunately, the retention capacity of MSCs in injured lung tissues is limited and this limits their capacity to repair injured tissues and restore pulmonary function. However, genetic modification of MSCs by overexpression of angiotensin type 2 receptors enhances the migration of MSCs to injured lung and increases the ability of MSCs to: (1) decrease the permeability of pulmonary endothelial cells, (2) downregulate the inflammatory reaction, and (3) promote restoration of structure as well as function of lung tissues [403].

Homing efficacy of MSCs can be improved by: (1) modification of the mode of administration by: heparin therapy, vasodilator treatment prior to MSC infusion, culture under hypoxemic conditions, and preconditioning of MSCs; (2) genetic modification by overexpression of: CXCR4 (C-X-C motif receptor 4) and integrin-α4; (3) cell surface engineering

to modulate the expression of adhesion molecules; (4) modification of the target tissue by using irradiation or manipulation of migration by ultrasound or magnetic and electrical fields; (5) caveats in modifying homing molecules by co-transplantation of HSCs and MSCs; (6) cultivation of MSCs with enhanced migratory ability by optimizing cell culture conditions or treatment of MSCs with a cocktail of cytokines including the use of IL-3; (7) enhancement of the ability of MSCs to respond to migratory stimuli; (8) modulation of physiological barriers that block MSC migration into the sites of injury; (9) stimulating the target site to recruit MSC mobilization, tissue preconditioning, or increasing tissue receptivity; (10) use of MSC-secretomes rather than pure MSCs; and (11) ensuring the presence of optimal environmental circumstances and metabolism for successful implantation of MSCs [405-411].

The off target homing of MSCs especially lodging in the lungs, which is usually considered a drawback of MSC therapy, may become very useful under certain circumstances such as COVID-19 related pneumonia, ALI, and ARDS [412]. Clinical applications of MSCs are dependent on their successful migration to the desired tissues following administration of these cells [404]. Unfortunately, homing of MSCs is inefficient with only a small fraction of systemically administered or infused MSCs reaching their target tissues [404,405]. Attenuation of lung inflammation and enhancement of lung protection against injury can be provided by inhibition of TNF signaling and overexpression of CXCR4 in MSCs [413,414].

Tracking of MSCs

Monitoring the location, distribution, and long-term engraftment of transfused or transplanted stem cells is critical to demonstrate success of stem cell therapy [415]. Recently, several techniques have been utilized to track transplanted or infused MSCs and these include: (1) high resolution CAT scanning, (2) conventional proton or fluorine 19 magnetic resonance imaging, (3) positron emission tomography scans, (4) single-photon emission CAT scans, (5) bioluminescence imaging, (6) multiple photon microscopy, and (7) time-gated fluorescence imaging [412,415-426]. After stem cell labelling with: (1) nanoparticles: magnetic nanoparticles, superparamagnetic iron oxide nanoparticles, and gold nanoparticles; (2) nanodiamond; and (3) silica-coated magnetic particles, tracking of stem cells is usually performed to determine their fate and to provide clear picture on their homing, biodistribution, viability, proliferation and differentiation [416,418,420,425,427,428]. Several cellular labelling techniques are available and they include: simple incubation, free organic dyes, use of transfection agents using viral or non-viral vectors, magnetoelectroporation, magnetosonoporation, and use of nanoparticles including organic dye, gold, and superparamagnetic iron oxide [420,425,428]. Synergy between size, structure, and physical properties of nanoparticles makes them key players in monitoring the fate and performance of infused stem cells [415].

Homing efficiency of MSCs depends on the specific nature of the targeted tissues and homing ability is important for MSCs to perform or execute their functions [370]. However, homing is a multistep process that includes: (1) tethering and rolling with initial tethering by selectins, (2) activation by cytokines, (3) firm adhesion or arrest by integrins, (4) diapedesis or transmigration using matrix remodelers, and (5) chemotaxis in which there is extravascular migration toward chemokine gradient [370,404,405].

Production and Manufacture of MSCs

Stem cells could be used in cell therapy either as massively produced allogeneic cells or as autologous stem cells [321]. The main differences between allogeneic and autologous manufacturing approaches are the number of therapeutic doses generated in each patch and the number of patients treated [429]. MSCs obtained from their main sources; BM, AT, PB, UCB, and placenta; exhibit the following features: multipotency, expansion potential, adherence to plastics, transient paracrine function, and immunomodulatory properties [321]. However, MSCs obtained from various sources have slight differences regarding their phenotype, telomere activity, and clonogenic capacities [430].

The main obstacles facing the utilization of tissue-derived MSCs are: shortage of tissue sources, difficult and invasive retrieval methods, heterogeneity of cell populations, low purity, cell senescence, and loss of pluripotency and proliferative capacities over continuous passages [322]. However, MSCs obtained from the Whaton's jelly of the UC have more advantages over MSCs obtained from other sources once it comes to: availability, abundance, ease of collection, and high expansion potential [430]. Compared to tissue-derived MSCs, MSCs derived from pluripotent stem cells have superior: large scale production, proliferative capacity, longevity, as well as immunomodulatory functions and this makes them ideal candidates for therapeutic applications in regenerative medicine [322]. MSCs obtained from the BM of geriatric patients can proliferate and can be cryopreserved without loss of viability and this makes these cells readily available for the treatment of elderly individuals with organ dysfunctions and tissue injuries [431].

Upstream processing (USP) and downstream operations cover: cell expansion, cell harvesting and purification, detachment and separation, washing and concentration techniques, and regulatory demands [321]. Various economic studies have demonstrated that USP; and human MSC expansion in particular; represents the main cost drivers in the entire manufacturing process [429]. Standardization of protocols and procedures for: production of MSCs, cell expansion, release of cells, therapeutic application, and quality control are essential components for the utilization of MSCs in various fields [430,432]. The application of good manufacturing practice to MSCs must ensure that clinical trials are not affected by: inadequate safety, quality, and efficacy arising from unsatisfactory manipulation of these stem cells [432].

Cryopreservation and Banking of MSCs

Cryopreservation using dimethyl sulfoxide as cryoprotectant has been successfully used for long-term storage of various types of stem cells including MSCs and it is considered the most effective method of cell preservation. However, there is a real need to further improve cryopreservation techniques [433]. Banking of allogeneic MSCs has been active for more than 11 years and several banks for cryopreservation of UCB-MSCs have been established worldwide [434,435]. Banked or cryopreserved UCB-MSCs have been shown to retain their biological properties including: morphology and specific surface markers, plastic adherence, and multipotent differentiation [436].

The objectives of establishing MSC banks include: (1) availability of high quality and well characterized MSCs for clinical applications, (2) establishment of functional capabilities of cells that are cryopreserved for long periods of time, (3) optimization of the number of cells available for clinical use and research purposes, and (4) documentation of procedures performed and keeping high standards and quality control of cell products [437]. Freshly thawed MSCs that have been cryopreserved maintain their: multipotent differentiation capacity, immunomodulatory functions, anti-inflammatory properties, and morphology as well as surface marker expression [438,439]. However, cryopreservation may deleteriously affect other functions and specific aspects of MSCs such as viability, attachment and migration, genomic stability, and paracrine function but 24 hours after thawing, MSCs recover some of these diminished or lost functions [438,439].

MSCs derived from UC tissues and obtained from multiple donors have the following advantages: (1) ease of harvesting or collection, (2) consistent proliferation and growth characteristics, and (3) consistent therapeutic properties. Therefore, these cells represent a consistent, reliable, and cost-effective source of MSCs for therapeutic applications [440]. It is essential to adhere to the FDA stem cell banking and storage standards and to follow the best industry practice guidelines with respect to: (1) proper collection, manufacture, and release criteria; (2) cryopreservation and storage; (3) shipping and delivery; and (4) logistic management of the final product in order to: reduce research costs, improve effectiveness, decrease time to discovery, and increase the number of approved marketed cell products [433].

MSC Therapies in COVID-19

There are two published studies from China on the use of MSCs in the treatment of COVID-19: one included 7 patients and the second one was a single case report [31-33]. Unfortunately, there are no reported studies on the use of other types of stem cells such as HSCs, ESCs, and iPSCs in the treatment of COVID-19. However, the use of other cells including the following immune cells may be considered for use in COVID-19 infection: mononuclear cells, DCs, NKCs, cytotoxic T-cells, and cytokine-induced killer cells [33]. Despite including small numbers of patients, the 2 recently published studies clearly show the usefulness of MSCs in the treatment of pneumonia and ARDS caused by COVID-19 [31,32,34].

The first study on the use of MSCS in COVID-19 pneumonia; Leng Z, et al. was a single center, open label pilot study that was performed at YouAn Hospital in Beijing, China [31,33,369]. Seven patients were included: 1 was labelled as critically severe, 4 as severe type, and 2 were labelled as common type. Three patients served as control group and they received placebo. MSCs were suspended in 100 ml saline and injected over 40 minutes. BM-MSCs were supplied by the University of Shanghi. MSCs at dose of 1×10^6 cells/kg body weight were administered IV. Patients were repeatedly evaluated till day 14 of MSC infusion. The results were as follows: (1) symptoms and pulmonary function tests significantly improved within 2 days of MSC infusion; (2) 3 patients recovered and were discharged within 10 days of therapy; (3) the following results were encountered during follow-up: lymphocytic count increased in the PB; CRP decreased; CD4+ T-cells, CD8+ T-cells, and NKCs disappeared within 3-6 days; DCs dramatically increased; IL-10 increased; and TNF-α significantly decreased. Another important result was that gene expression profile showed that MSCs were ACE2 negative and TMPRSS2 negative implying that MSCs were free from COVID-19 infection. The authors concluded that IV administration of MSCs was safe and effective in the treatment of COVID-19 pneumonia particularly in patients with severe infection [31,33,369].

The second study was a single case report. Liang B, et al. reported that a 65 year old female deteriorated after having COVID-19 infection, then she was shifted to the ICU [32,369]. She received mechanical ventilation for having severe pneumonia and ARDS manifested by bilateral pulmonary infiltrates. She received antibiotics, antiviral, and steroids but without response. Then she had further deterioration and she developed multiorgan failure including liver dysfunction. Allogeneic human UCB-MSCs were administered: 3 IV injections (each dose: 5×10^7 cells) were given 3 days apart. The following laboratory results were obtained: reduction in severely elevated neutrophils, increase in lymphocytic count, and progressive increase in CD3, CD4, and CD8 cells. Additionally, clinical and radiological recovery reflected the successful management [32,369].

Recently, 2 commercial companies made press releases announcing their preliminary results on the use of MSCs in the treatment of patients having severe COVID-19: (1) on Apr 7, 2020; Pluristem reported MSC treatment of 7 patients with COVID-19 having ARDS and receiving mechanical ventilation in ICU and they announced 100% survival rate and 66% improvement in respiratory parameters; and (2) on Apr 24, 2020; Mesoblast reported the compassionate use of allogeneic MSCs in the treatment of 12 patients with COVID-19 having moderately severe ARDS and they announced 83% survival rate and that 75% of patients came off ventilator support within 10 days of MSC administration [369,441,442].

In May 2020, a team from United Arab Emirates stem cell center in Abu Dhabi reported the use of stem cells; most likely MSCs; to treat patients having COVID-19 pneumonia and ARDS. They harvested the stem cell from the PB of patients, then after processing and manipulation of the stem cell products, they gave the stem cell by inhalation using nebulizers. Other therapeutic protocols were continued. The team reported successful management of 73 patients with COVID-19. This was announced to the media but has not yet been published in any medical journal [443].

In China, at least 4 clinical trials on the use of MSCs in the treatment of COVID-19 pneumonia, mainly using UCB-MSCs were registered in February and March 2020. The results of these trials will be published in the near future and they will determine the efficacy of MSC therapies in COVID-19 infections [25]. Currently, MSCs are being tested in several clinical trials including: NCT04269525, NCT04288102, and NCT04252118 [14,29,33,371].

Requirements and Rationale for Using MSCs in COVID-19

In the race for using MSCs in the treatment of COVID-19, it is vital to only use well-characterized MSCs via safe delivery methods as well- characterized MSCs with robust manufacturing procedures and optimized modes of clinical delivery hold great promise in ameliorating COVID-19 infection by: exerting their beneficial immunomodulatory and antimicrobial effects, and inducing tissue repair as well as organ protection [444,445]. Additionally, the following are required before adopting MSCs in the treatment of COVID-19 infections: (1) updated guidelines on the use of cellular therapies in infectious diseases in particular; (2) updated minimal criteria for characterization of cellular therapies; (3) updated cell therapy routines that reflect specific needs of patients requiring this form of treatment; and (4) the use of ACE2 negative MSCs in the treatment of patients with COVID-19 having ALI and ARDS [444-446].

In the era of COVID-19 pandemic, several groups of scientists from all over the world with experience in MSC therapies have suggested the use of MSCs and their secretomes in the treatment of severe COVID-19 infections as MSCs and their secretory products have the following beneficial effects: (1) suppression of viral replication, viral shedding, and virus-induced damage to lung epithelial cells; (2) enhancement of the generation of regulatory T-cells that are suppressed by COVID-19; (3) MSCs shift the phenotype of antigen presenting cells including DCs, B-lymphocytes, and macrophages; (4) MSCs modulate the proliferation and activation of naïve and effector T-cells, NKCs, and mononuclear cells; (5) MSCs prevent the formation of NETs that may have deleterious effects in patients with COVID-19 pneumonia and ARDS; (6) MSCs can inhibit the cytokine storm induced by COVID-19; (7) secretomes of MSCs including ECVs and exosomes have antiviral, antibacterial, and even analgesic effects; (8) reduction in pulmonary edema associated with ARDS in COVID-19; (9) entrapment of IV infused MSCs in the lungs which is an advantage in patients with COVID-19 patients having pneumonia and ARDS; (10) enhancement of tissue regeneration and promotion of endogenous repair and healing in ALI induced by COVID-19; and (11) safety and efficacy of MSCs and their products provided good manufacturing practice guidelines and quality control measures of the whole process from harvesting till delivery are strictly applied [25,26,29,33,34,369,444,446-455].

Conclusion

The numbers of patients infected with SARS-CoV-2 virus and those dying from the complications of COVID-19 are rapidly increasing on daily basis without having specific therapies or vaccines. Meanwhile, treatment of patients having COVID-19 relies mainly on supportive care and drug repurposing. However, the search for curative therapy by developing new drugs and manufacturing vaccines continues although developments of new therapeutic agents and vaccines are time and effort consuming.

MSCs and their secretory products appear to have a promising role in the management of COVID-19 complications such as pneumonia, sepsis, ALI, and ARDS. They can be obtained from various sources and they can be administered via different routes. Additionally, MSCs can be used in conjunction with other therapies given to treat COVID-19. However, plenty of efforts are urgently needed to standardize the use of MSCs and their secretomes in various infectious diseases and in COVID-19 in particular.

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