COVID-19 and Strategies for Its Therapeutics

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ABSTRACT: Currently the epidemic of SARS-CoV-2-caused COVID-19 is a major threat to global public health. The latest clinical data, laboratory results, and autopsy information are summarized herein to provide a brief review of the significant issues surrounding SARS-CoV-2 and COVID-19. In this review, we also cover research on the ways in which the virus enters the human body, general clinical symptoms, immunopathological responses in severe cases of COVID-19, and the issues surrounding the potential therapeutic responses to the illness.

KEY WORDS: COVID-19, SARS-CoV-2, therapeutics, clinical trial, vaccine

I. THE ONGOING WORLDWIDE EPIDEMIC OF COVID-19

Currently, people throughout the world are suffering from a highly contagious plague caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with an average mortality rate of 3.06% (979,212 out of 32,029,704). This is devastatingly high, particularly for countries such as the United Kingdom, where 41,862 out of the total 409,733 certified cases (10.21%) were killed by coronavirus disease (COVID-19). The current mortality rate for the United States, as reported by the World Health Organization (WHO), is 2.92% (200,725 out of 6,868,828 confirmed cases) as of September 25, 2020.¹ Although these high mortality rates are not expected to be maintained as testing becomes more widely available, the impact of the increasing total numbers of confirmed cases is nonetheless dreadful for everyone. Scientists throughout the world are working tirelessly to identify effective and safe therapeutics for the pneumonia caused by SARS-CoV-2, including vaccine development, assessing the potential use of statins, anti-HIV drugs, and immune-based therapies.

II. THE VIRUS'S ENTRY INTO THE HUMAN BODY: JUST THE BEGINNING

In December 2019, the virus strain of SARS-CoV-2 was first isolated from the human airway epithelial cells and was later identified as a new clade within the sarbecovirus subgenus. SARS-CoV-2 is a positive-sense single-stranded RNA virus and is the seventh most infectious member in the coronavirus family.² The genome of the virus was compared with SARS-CoV and MERS-CoV, and the homology was about 79% and 50%, respectively. Thus it was named as novel coronavirus, or SARS-CoV-2.³ Generally, SARS-CoV-2 is structurally composed of spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid (N).

Human angiotensin converting enzyme 2 (ACE2) is well-known for its role in the renin-angiotensin-aldosterone system, which is essential for the regulation of systemic blood pressure and renal function. Increasing evidence has added a level of complexity to ACE2's new functions in pathological processes, for which it serves as a receptor for direct binding with different strains of coronavirus, including SARS and NL6.⁴ The highly infectious nature of coronavirus stems from the high binding affinity

between ACE2 and the receptor binding domain (RBD) of SARS-CoV-2 S proteins. The entry process is also facilitated by transmembrane protease serine 2 (TMPRSS2) exposing a fusion sequence, a fundamental step for the binding-fusion-entry processes.⁵ In the cells infected by coronavirus, the pathogen-associated molecular patterns (PAMPs) of the viral nucleic acids are sensed and recognized by specific pathogen recognition receptors (PRRs). RIG-1s, like helicase MDA5, PKR, and OAS, are involved in the recognition events.⁶ The interferons could be produced by the infected epithelial cells and induce innate immune responses, and the TLR3/TLR4 adaptor TRIF participates in the immune responses after the SARS-CoV infection.⁷

ACE2 has been identified as the receptor for SARS-CoV-2 to enter human lung cells,^{8,9} which is expressed in multiple human organs, such as certain cell types within the pulmonary, intestines, kidney, heart, and testis.¹⁰ This may explain why viral particles can be detected in the expectorations, feces, and semen of the infected population, and consequently, semen and prostate secretion should also be further explored.^{11–13} The wide distribution of infections possibly could be explained by a recent *in vitro* study in which host cells were infected and manipulated to bud filopodia protrusions carrying viral particles to infect the surrounding cells; the CK2 was also contained in the protrusions.¹⁴

Extended human activities occupied and caused permanent damage to the territories of wild animals, which possibly broke the strict infectivity barriers between humans and species of bats. In recent years, many novel strains of the virus have been identified in wild animals like Chinese horseshoe bats,¹⁵ showing varying degrees of homologies of the already-known contagious virus; these should be monitored to prevent the outbreak of new rounds of virus-induced epidemics.^{16–18}

III. THE CLINICAL SYMPTOMS OF COVID-19 AND UNDERLYING MOLECULAR ATTRIBUTES

The common clinical symptoms of COVID-19 are mainly caused by abnormalities in the respiratory system, gastrointestinal system, and cardiovascular system. Other symptoms from thrombotic

complications are also commonly observed in COVID-19 patients (Fig. 1). Different levels of severity are also observed in COVID-19 patients, with more than 80% of patients only experiencing mild to moderate symptoms, without the need for hospitalization.¹⁹

The existence of viral particles has been recorded in respiratory, feces, and other samples (Fig. 1),^{11–13} and the nasal tract was proposed as the first viral bank for invasion into the human body.²⁰ Higher viral loads were found in the nasal swab compared with pharyngeal ones.¹¹ Thus the fluids and secretions from the nose should be properly managed to avoid further infections, and mask protections are strongly recommended for high-risk districts. However, a negative nasopharyngeal swab test does not guarantee that an individual is free of viral infection, for in some postmortem tests of COVID-19 patients, the viral nucleic acid was shown to be negative.²¹ Thus the swab test and blood test should be combined to increase the accuracy of screening and diagnosis.

The first three reported COVID-19 patients showed the clinic symptoms of fever and cough, and with bilateral fluffy opacities in chest radiographs, 7 days after the initial report of discomfort on December 20, 2019. One patient developed respiratory distress and died on January 9, 2020, only 20 days from the onset of clinical symptoms, thus indicative of the rapid nature of the disease's progression.² A relatively detailed investigation was performed in a cohort of 41 hospitalized patients with COVID-19. It only took an average of 2 days from hospital admission to acute respiratory distress syndrome (ARDS), and 15% patients died from this. All 41 patients had pneumonia, presenting in CT images as ground-glass opacities.²² The most common clinical symptoms were fever (98%), cough (76%), fatigue (44%), and dyspnea (55%).²² In another bigger cohort study, 452 patients with COVID-19 were recruited; fever (92.6%), shortness of breath (50.8%), fatigue (46.4%), expectoration (41.4%), dry cough (33.3%), and diarrhea (26.7%) were the most common symptoms.²³ The underlying mechanism and exact pathological changes should be clarified as soon as possible.

FIG. 1: Common clinical symptoms of COVID-19 in the respiratory system, gastrointestinal system, and CNS system, along with other symptoms from thrombotic complications. The different levels of severity were also observed in COVID-19 patients (cited image of the male body is available from <https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue#checkbox>).

In the serum of COVID-19 patients, increased levels of IL-1, IL-2, TNF- α , and IL-6 all served as endogenous pyrogen, acting on the thermoregulation center hypothalamus, increasing the body temperature for more effective immune response, and finally causing fever, as is common in COVID-19 patients.²³ IL-1 β associates with hyperalgesia (increased sensitivity to pain) were also increased in COVID-19 patients, probably underlying the myalgia symptoms of the patients.²³ The increased neutrophil-to-lymphocyte ratio (NLR) and levels of procalcitonin cause potential bacterial coinfection due to the dysfunctions of the immune system in COVID-19, which could possibly cause pneumonia in the lung.²³ In addition, the high serum level of C-reactive proteins (CRP) in COVID-19 patients also increased, which is possibly caused by macrophage activation syndrome and bacteria coinfections, but not common in virus infections.²⁴

The incidence of diarrhea was more frequent (26.7%) in the cohort of 452 COVID-19 patients; this could possibly be explained by ACE2 as a common receptor for SARS-CoV-2 and SARS-CoV, highly expressed in the gastrointestinal tract.¹⁰ The ACE2

expression in lung tissue is at a much lower level than it is in the intestine.¹⁰ In addition to ACE2 and TMPRSS2, other unknown mechanisms facilitating the entry of the virus into mammalian cells warrant further exploration to clarify why the lower respiratory tract is the most commonly injured site, aside from the upper respiratory tract. Recent research has challenged the idea that the lower respiratory tract is a major targeted site, with evidence demonstrating higher infectivity in the nose compared with the lower pulmonary sites, along with a higher expression of ACE2 in the nasal cavity versus the lower part of the respiratory tract.²⁰ This is also supported by the fact that the SARS-CoV-2 entry-associated genes ACE2 and TMPRSS2 are co-expressed in the nasal epithelial cells with genes involved in innate immunity.²⁵ This evidence indicates that the initial infected site may be concealed by the light symptoms associated with it and that the nasal cavity is the potential initial viral base, providing puffs of viral particles to the lower respiratory tract through aspiration.

In COVID-19 patients, increased coagulated factors of D-dimers indicate that it is possible to

develop a state of hypercoagulation. Furthermore, increased TNF- α and IL-1 could induce endothelial cells and lymphocytes to secrete nitric oxide and reactive oxygen species, which could affect blood coagulation, cause tissue damage and disseminated intravascular coagulation (DIC),²⁶ and also increase the risk for thrombosis in parts of the vessels, lungs, catheters, and microvascular vessels in the toes.^{27–31} As more clinical and autopsy data become available, potential associations between COVID-19 and a variety of embolism syndromes have been cited,^{32–34} likely caused by immunological responses. The prevention of venous thromboembolism (VTE) is recommended only for those who experience an incident thromboembolic event or who are highly prone to have thromboembolic conditions.³⁵

Evidence has shown that a high load of virus particles could be detected in the asymptomatic population, indicating the high infectivity and uncertain patent period of the coronavirus. One seroepidemiological study in the Spanish population indicated that at least one-third of the infected population were without typical symptoms of COVID-19.³⁶ In asymptomatic individuals and patients who recovered from COVID-19, levels of IgG and neutralizing antibodies decreased approximately 2–3 months after initial infection with SARS-CoV-19, thus placing this population at risk of being superinfected.³⁷ And, new strains of SARS-CoV-19 with certain mutations are likely to increase the risk of reinfection.

IV. AUTOPSY AND PATHOLOGICAL CHANGES IN COVID-19 PATIENTS

SARS-CoV-2 infection and uncontrolled immune responses cause extensive damages in multiple organs of the severely infected.²¹ The clinical autopsy of 91 COVID-19 victims indicated that the most serious pathological changes were located in the respiratory system, with prominent and extensive pulmonary lesions. Respiratory tract lesions were caused by mucosa congestions in the trachea and bronchus, together with focal epithelial pneumocytes exfoliation. The diffuse alveolar lesions included a hyaline membrane formed by serous and fibrin exudate filling the cavity of the alveoli. Some septal rupture and cystic cavity of the alveoli were

potentially caused by clear dilations of the alveoli. And, the thickening of the alveolar walls was possibly caused by stimulations of the accumulated alveolar fluids and hyperplasia of type II pneumocytes. Exudative inflammation also existed in the parenchymal areas, causing interstitial fibrosis and pulmonary carnification. In addition, focal pulmonary hemorrhagic infarction and thrombosis may be caused by the accumulation of mucin plugs in the microvessels. Coronavirus particles were seen at the site of pulmonary lesions, like in the tracheal and bronchial mucosa epithelia, and type II alveolar pneumocytes, together with the expression of ACE2 in these cells. Under a microscope, the infiltration of monocytes and macrophages was seen in the alveoli. ACE2 is expressed in the infiltrated macrophages. The formation of neutrophil extracellular traps (NETs) could strongly contribute to acute lung injury during virus infection,^{38–40} so dornase alfa was recommended to decrease mucus rigidity and accumulation in severe COVID-19 patients by degradation of the extracellular DNAs.⁴¹ The pathological changes of the accumulated pulmonary mucus were also evidenced in CT images.⁴² All the above pathological changes account for ARDS and greatly obstruct ventilation, especially in the small airways, eventually leading to the suffocation of COVID-19 patients.

Multiple types of cells within the affected organs are susceptible to impairment in COVID-19 patients. These damaged areas contain certain types of cells that could be directly infected by SARS-CoV-2. A variety of pathological lesions were observed in organs of multiple systems in autopsy examinations. Viral particles could be detected in most of these impaired organs, including the trachea and lung in the respiratory system; the heart and blood vessels in the cardiovascular system; the spleen and lymph nodes in the immune system; the liver, esophagus, gastrointestinal tract, gallbladder, and pancreas in the digestive system; the kidney, breast, and testis in the urinary and genital systems; and the adrenal gland in the endocrine system. Some organ damage can be monitored via clinical tests—for example, kidney damage in COVID-19 patients could be indicated by continuously increasing levels of urea nitrogen and creatinine in severe cases.⁴³

Thus the support of multiple organs should be emphasized and performed in clinic therapeutics for the severe COVID-19 patients.²¹

V. IMMUNOLOGICAL CHANGES IN COVID-19 PATIENTS

Major immune responses in severe cases of COVID-19 are characterized as uncontrolled cytokine storm, exhausted lymphocytes, lymphopenia, and high NLR.⁴⁴ Macrophages, neutrophils, and dendritic cells, together with the IgA-containing mucosal barriers, serve as the frontier barrier against SARS-CoV-2 infection.⁴⁵ Impaired inflammatory responses in severe COVID-19 patients provided a distinct pattern of pathological progression,^{23,44,46–48} and the clinical symptoms of the noted immunological deteriorations are ARDS, septic shock, and multiple organ failure (MOF).⁴⁹ The molecular mechanisms underlying immunological manifestations in severe COVID-19 patients should be further explored and clarified. Figure 2 illustrates the

possible immunological changes that occur with potential symptoms.

A. Cytokine Storm

The serum proinflammatory cytokines and chemokines, such as IL-6, IL-1 β , IL-2R, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP-1, MIP-1 α , and TNF- α , were significantly increased in severe COVID-19 patients; these cytokines recruit immune cells through a positive feedback loop, eventually causing a cytokine storm.^{23,50,51} The proliferation of macrophages in multiple tissues was observed,²¹ with the presence of IL-6 in plasma as a hallmark of severe infections. Cytokine storm was also found to be the major cause of morbidities in patients with SARS-CoV and MERS-CoV.⁵²

IL-6 is a stable indicator of poor outcomes and severity, and the use of mAb tocilizumab against IL-6 has achieved positive clinical outcomes and benefits, even in severe cases of COVID-19.^{53,54} IL-6 inhibitors are not recommended at this time,

FIG. 2: Clinical symptoms and immunological changes in COVID-19 patients

due to insufficient data from clinical trials.⁵⁵ IL-6 could promote IL-17 production by CD4⁺ T cells, and STAT3 and NF- κ B signaling pathways are involved in this process.⁵⁶ Reciprocally, IL-17 induces the production of IL-6, IL-1 β , TNF- α , G-CSF, GM-CSF, IL-8, and MCP-1. IL-17 attracts infiltrations of neutrophils into alveolar tissues and remodels the airway, and it is essential for the functions of Th17 cells.^{57,58} IL-17 receptors are widely dispersed in multiple tissues, such as the kidney, intestine, and heart.

IL-1 is mainly produced by macrophages, neutrophil, monocytes, DC cells, and many other types of cells. It could activate and promote the functions of CD4⁺ T cells, B cells, monocytes, and macrophages; attract neutrophils; and induce the secretion of inflammation mediators. However, due to insufficient clinical data and no data from clinical trials on the administration of anakinra (IL-1 inhibitors) in COVID-19 patients, there is no recommendation for the use of IL-1 inhibitors.⁵⁹

IL-2 is produced by T cells and stimulates the proliferation of T cells. IL-2 could promote NK cell functions to kill virus-infected cells. Increased IL-2R could possibly inhibit the activation of T cells in COVID-19 patients.²³

IL-8 is a neutrophil chemotactic factor produced by mono-macrophages. IP-10 (CXCL10, CRG-2) attracts Th1 cells, eosinophils, monocytes, and NK cells to the site of inflammation. It is upregulated by activated T cells, neutrophils, splenocytes, keratinocytes, osteoblasts, astrocytes, endothelial cells, smooth muscle cells, and pancreatic beta cells. MCP-1 (CCL2, JE) is a chemokine that binds to the receptor CCR2 and induces the chemoattraction of mononuclear cells. It induces the activation of monocyte, NK cells, lymphocytes, and basophil. Additionally, CCL2 promotes Th2 polarization in CD4⁺ T cells and CCL2-mediated recruitment of monocytes to the inflammation sites. MIP-1 α (CCL3) acts as a chemoattractant to a variety of cells, including monocytes, T cells, B cells, and eosinophils. TNF- α is produced by monocytes and macrophage, and TNF- β is majorly produced by activated T cells. TNF plays an important role in killing infected cells, inducing apoptosis and immune and inflammation responses. Increased GM-CSF in COVID-19

patients could stimulate stem cells to produce granulocytes (neutrophil, eosinophil, and basophils) and monocytes. Monocytes exit the circulation and migrate into tissue, whereupon they mature into macrophage. G-CSF has the same function, stimulating the hemopoietic progenitor cells to differentiate into granulocytes and monocytes. G-CSF and GM-CSF continuously stimulate hemopoietic progenitor cells to produce more lymphocytes to supply the shortage of immune cells for effective immune responses.

IFN-gamma is produced by T cells and NK cells. It plays an important antiviral role, and levels were decreased in COVID-19 patients. IFN responses in COVID-19 patients could potentially be interfered with, mainly by escaping viral recognition through PAMP⁶⁰; evading activations of host responses through targeting the polyuridine sequences by coronavirus endoribonuclease⁶¹; methylation on ribose-2'-O of virus RNA, avoiding MDA5 recognition⁶; and deubiquitination by papain-like proteinase to alleviate the response of interferon.⁶² Type I interferon could also be inhibited by M protein via deterring the assembling of the TBK1/IKK, TRAF3, and TANK complex, which may be the same as the process for SARS-CoV-2.⁶³ The structural M protein of the coronavirus as a structural PAMP could enhance the responses of type I interferon through Toll-like receptor (TLR)-related mechanisms.⁶⁴

The cytokine storm could lead to septic shock and whole system damage, particularly attracting the infiltration of neutrophils and macrophages into pulmonary alveoli and tract. Continuously expressed cytokines and chemokines could cause damages or even failures in multiple organs of COVID-19 patients. Glucocorticoid therapeutics against overactivated inflammation responses were recommended for severe cases.⁶⁵

B. Lymphopenia

Lymphopenia is characterized by remarkably decreased T cells, B cells, and NK cells, along with decreased monocytes, eosinophils, and basophils.²³ Reduced CD4⁺ and CD8⁺ T cells were observed in the tissue of the spleen and lymph nodes, and lymphocyte degeneration and necrosis were also observed.²¹ In the immune organs of the spleen and

lymph nodes, virus particles and RNA were positively identified. Atrophic spleens with hemorrhage, anemic infarctions, and interstitial hyperplasia were visible.²¹ Lymph node damages were also observed in deceased patients, with apoptotic and necrotic lymphocytes, and hyperplasia interstitials dispersed in the paracortical and follicle areas.⁶⁶ This evidence indicates that the immune organs were likely directly attacked by SARS-CoV-2, and the lymphocytes were deeply impaired or killed.

In terms of the most influenced subsets of T cells, the counts of helper T cells, suppressor T cells, memory helper T cells, and regulatory T cells were all decreased, but a portion of naïve helper T cells were increased.²³ The transformation of naïve CD4⁺ T cells to effector and memory T cells is an essential process in adaptive immunology. A higher naïve T cell to memory T cell ratio indicates a poorly functioning immune system in severe COVID-19 patients.²³ The counts of CD4⁺ T cells, CD8⁺ T cells, and regulatory T cells decreased; these subtypes of T cells play an important role in controlling overactivated innate immune responses in viral infection.⁶⁷ NK cells and CD8⁺ T cells exhibit functional exhaustion patterns with increased expression of NKG2A, PD-1, and TIM-3, which are exhaustion markers and return to normal in patients who have rehabilitated.⁶⁸ This evidence indicates that the number of cytotoxic lymphocytes decreased and their functions were exhausted too.

The consumption or low production of lymphocytes, along with the exhausted functions of NK cells and T cells, were indicative of impaired adaptive immune responses, which further aggravated uncontrolled inflammatory responses in severe COVID-19 patients. Several questions remain here: Why does lymphopenia happen? And where do the lymphocytes go? Furthermore, are they attracted to certain tissues and sites of inflammation and then trapped? It was reported that lymphocytes from recovered patients were not new cells after the viral infection; rather, because of the temporal sequestration of the lymphocytes, they were circulated between peripheral blood and tissues or organs.⁶⁹ The results of an *in vitro* study indicated that SARS-CoV-2 infection could promote MAPK signaling and inhibit the mitotic kinases to arrest the

cell cycle,¹⁴ possibly accounting for lymphopenia in COVID-19 patients. It is also possible that unknown factors induced more production of neutrophils and monocytes, which occupied too many biological resources for the progenitor cells to differentiate into lymphocytes. In addition, the lymphopenia and decreased adaptive immune responses were possibly caused by the downregulation of antigen presentation via MHC-I and MHC-II molecules after SARS-CoV-2 infection.²⁴ The exact molecular mechanisms should be discerned to clarify the immunopathological causes for the lymphopenia of COVID-19. Thus a specific strategy of therapeutics is proposed that involves enhancing adaptive immune functions, with a particular focus on the number and abilities of T cell subsets and controlling overactivated inflammatory responses like cytokine storms in COVID-19 patients.

C. Adaptive Immune System and Antibodies

IgM should be produced in the early stage of infection as the first apparent antibody, but IgG also appeared simultaneously in COVID-19 patients. IgG is the main driver of the body's immune response against microbes, binding the antigens on the infected cells. Increased IgG responses could activate the complement system and cause damages in the virally infected cells by the formation of MAC. Serum levels of IgA, IgG, and IgM and components of the complement system (as C3 and C4) were in the normal range in severe COVID-19 patients. Mucosal IgA or sIgA in the excretion form serves as the first physical barrier in the gastrointestinal and bronchus, which can bind the virus to avoid viral invasion. Increased IgA responses were observed in severe COVID-19 patients⁷⁰ and tended to be stronger than IgM responses.^{71,72}

A higher titer of antibodies was reportedly correlated with the severity of COVID-19. In the early stage of the onset of COVID-19, SARS-CoV-2-specific antibodies could be detected in patients.⁷³ The neutralizing antibodies in patients' plasma has been utilized for clinical therapeutics.⁷⁴ In the recovery immunological processes, the role of antibodies is either protective or pathogenic, which remains

uncertain. Thus the promotion of application of convalescent plasma for clinical therapeutic purposes is at high risk. Indeed, a potential antibody-dependent enhancement (ADE) has been shown in cases of MERS.⁴⁴

The coagulation system, kinin system, fibrinolysis system, activated neutrophils, endothelial cells, and platelets, together with TNF- α , IL-1, and IL-6, form an inflammation-mediated system in COVID-19 patients. An overactivated host immune system is responsible for the quick deterioration of COVID-19 patients.⁴⁹ A sustained state of overactivated immune responses could lead to death if it is not alleviated immediately.²² Male patients with old age and basic chronic diseases like diabetes and hypertension are more likely to deteriorate; these complications worsen the disease outcomes, possibly due to this population's lower capacity for immunological defense.⁷⁵ This evidence only further enhances recommendations for healthy living habits and regular exercise to boost immunological abilities.

VI. CURRENT ISSUES WITH POTENTIAL THERAPEUTICS FOR COVID-19

As we have seen in the past few months, a lack of effective therapeutics has put the entire world population at risk for COVID-19. Many infected individuals will potentially move from mild to severe cases and ultimately death due to a general lack of sophisticated support facilities in many parts of the world. On June 30, 2020, the U.S. Centers for Disease Control and Prevention issued an "Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease" report, indicating that there are currently no antiviral drugs licensed by the U.S. Food and Drug Administration (FDA) for the treatment of patients with COVID-19. No available data from randomized controlled trials in humans support recommending any investigational therapeutics for patients with confirmed or suspected COVID-19, although the use of remdesivir has been cleared by the FDA as an Emergency Use Authorization (EUA).⁷⁶ The currently adapted clinical management of COVID-19 patients is therefore mainly supportive care of complications, including

advanced organ support with endotracheal intubation and mechanical ventilation and extracorporeal membrane oxygenation (ECMO), along with some effective or potentially effective therapeutics (Table 1).

As noted previously, among the therapeutics currently being used clinically, as well as those being investigated in clinical trials, is one promising antiviral drug known as remdesivir. On May 1, 2020, the FDA announced an EUA for remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe symptoms. Remdesivir was evidenced in a clinical trial to shorten the time to recovery in some patients,⁷⁷ which is far from previous expectations. However, the clinical data on the safety and effectiveness of therapeutics with remdesivir for COVID-19 treatment are insufficient.

Another promising but disputed treatment is via an anti-malaria drug known as chloroquine, with many publications supporting the application for treatment of COVID-19.⁷⁸ However, in June 2020, the FDA revoked the EUA for the drug,^{79,80} based on results from a large, randomized clinical trial in hospitalized patients. The FDA found the medicine to show no benefit for decreasing the likelihood of death or speeding recovery, which is quite astonishing and controversial based on previous evidence and publications.

In addition, the anti-inflammatory effects of glucocorticoids have been widely utilized to relieve inflammation severity in the lung for protective purposes. Some experts worried that the administration of steroids was of little benefit and might reversely suppress the overall immunological response and slow the clearance of viral particles from the body.⁸¹ Based on a randomized clinical trial, dexamethasone is the first medication shown to decrease mortalities by around one-third in COVID-19 patients. The administration of low-dose dexamethasone benefits severely ill COVID-19 patients but has shown no effect in mild to modest cases.⁶⁵ This further indicates that the administration of steroids should be used selectively in only severe cases, rather than in all COVID-19 patients with differing degrees of severity.

TABLE 1: Current therapeutic strategies for COVID-19: Recommendations, indications, and concerns

Therapeutics	Recommendations	Notes	Warnings
Remdesivir	For hospitalized patients with severe COVID-19 ⁷⁶	For patients with SpO ₂ ≤ 94% on ambient air or patients requiring supplemental oxygen, patients on mechanical ventilation or ECMO, patients not intubated; duration of therapy is 5 days ⁷⁶	Not clear for those who are not improved and mild to moderate COVID-19 patients ⁷⁶ ; no effect on deaths ⁷⁷
Dexamethasone	For severe COVID-19 patients ⁶⁵	Cut deaths by one-third in patients on ventilation; dying risk reduced by 20% in patients receiving oxygen therapy; 6 mg per day for 10 days ⁶⁵	No effect in less-severe COVID-19 patients not receiving oxygen or ventilation ⁶⁵
Convalescent plasma	No recommendations ⁸⁸	In some countries, for COVID-19 patients with rapid deterioration, severe COVID-19 patients in the early phase of rapid deterioration, not in the terminal phase with multiple organ failure cases ⁸⁹	Limited data from China indicate benefits to COVID-19 patients, with little data from rigorously controlled clinical trials ⁹⁰ ; potential ADEs ⁸⁸
Vaccines	For susceptible population	Under development or in clinical trials ⁹¹	Resistant mutations may reduce vaccine sensitivity ⁸⁵
IL-1 inhibitor	No recommendation ⁵⁹	Insufficient clinical data and clinical trial data	No recommendation for COVID-19 patients
IL-6 inhibitor	No recommendation ⁵⁵	Insufficient clinical data and clinical trial data	No recommendation for COVID-19 patients
Interferons (alfa, beta)	Against being used for COVID-19 patients ⁹²	Lacking clinical trial data, and only being suggested as a potential treatment for COVID-19, for <i>in vitro</i> and <i>in vivo</i> antiviral properties ⁹²	The toxicities of interferon outweigh the potential for benefit ⁹²
JAK inhibitors	Against being used for COVID-19 patients ⁹²	Baricitinib as a potent agent against the interferon-associated inflammatory ⁹²	The extensively immunosuppressive effects outweigh the potential for benefit

A mixture of neutralizing antibodies is currently being developed, showing satisfactory results. Some COVID-19 vaccines have already passed Phase I/II clinical trials with satisfactory outcomes. The first vaccine to enter clinical trial was a recombinant adenovirus type-5 (Ad5)–vectored vaccine expressing the spike glycoprotein of one SARS-CoV-2 strain. This vaccine stimulated the production of significantly increased neutralizing antibodies in healthy volunteers, peaking 28 days after injection; aside from this, only mild and moderate adverse effects were observed.⁸² mRNA vaccines also have entered

clinical trials. These vaccines exhibited several prioritized features, such as high biosecurity, mass production at high speed, and accessibility for a large population.⁸³

It has recently been reported that the ancestral viruses of type O were replaced by the evolved viruses of type A2a, with a mutation S-D614G.⁸⁴ The A2a type was discovered to be of high infectivity and fatality, sweeping across the globe, especially via the viral strains from Belgium, Spain, Italy, France, the Netherlands, and Switzerland, which top the death toll. Conversely, Kuwait and Germany, with a wild

type of S-D614G, have fewer casualties.⁸⁵ In addition, other mutations also exist as potential strains of the SARS-CoV-2 with unknown infectivity. Two major problems are posed by the evolving mutations: one is that vaccine development may become cyclical work; the other is that new strains of the virus possessing mutations like S-D614G are a threat to recovered COVID-19 patients in China. Newly confirmed cases in the Xinfadi food market of Beijing were identified as possessing mutations, with potentially high mortalities and infectivity. This evidence indicates that subtypes of SARS-CoV-2 should be considered in future vaccine developments.⁸⁶ There are several concerns regarding vaccine development, including the high failure rate of proposed vaccines, the fact that high numbers of neutralizing detectable antibodies do not necessarily translate to clinical protection, the continued appearance of genomic mutations, and the elusive nature of real protective efficiency.

Scientists throughout the world are working tirelessly to identify effective and safe therapeutics for the pneumonia caused by SARS-CoV-2, including vaccine development and drug development. Unfortunately, we have not yet reached a consensus about the most effective drugs or therapeutics to prevent the spread of this illness.⁸⁷ Without convincing positive results from rigorously designed clinical trials, the promotion of any therapeutics is irresponsible, including statements about the attenuation of clinical symptoms, fever reduction, and possible prevention of mild cases from increasing in severity to levels that are fatal for some. Consequently, immediate international action is called for to effectively address this pandemic and to better prepare nations for future pandemics.

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