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Review

COVID-19: Review of a 21st Century Pandemic from Etiology to Neuro-psychiatric Implications

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Abstract. COVID-19 is a severe infectious disease that has claimed >150,000 lives and infected millions in the United States thus far, especially the elderly population. Emerging evidence has shown the virus to cause hemorrhagic and immunologic responses, which impact all organs, including lungs, kidneys, and the brain, as well as extremities. SARS-CoV-2 also affects patients', families', and society's mental health at large. There is growing evidence of re-infection in some patients. The goal of this paper is to provide a comprehensive review of SARS-CoV-2-induced disease, its mechanism of infection, diagnostics, therapeutics, and treatment strategies, while also focusing on less attended aspects by previous studies, including nutritional support, psychological, and rehabilitation of the pandemic and its management. We performed a systematic review of >1,000 articles and included 425 references from online databases, including, PubMed, Google Scholar, and California Baptist University's library. COVID-19 patients go through acute respiratory distress syndrome, cytokine storm, acute hypercoagulable state, and autonomic dysfunction, which must be managed by a multidisciplinary team including nursing, nutrition, and rehabilitation. The elderly population and those who are suffering from Alzheimer's disease and dementia related illnesses seem to be at the higher risk. There are 28 vaccines under development, and new treatment strategies/protocols are being investigated. The future management for COVID-19 should include B-cell and T-cell immunotherapy in combination with emerging prophylaxis. The mental health and illness aspect of COVID-19 are among the most important side effects of this pandemic which requires a national plan for prevention, diagnosis and treatment.

Keywords: Alzheimer's disease, coronavirus, COVID-19, COVID-19 diagnostics, COVID-19 test, mental health, SARS-CoV-2, SARS-CoV-2 treatment, Remdesivir, Hydroxychloroquine, Avigan, Actemra, COVID-19 Nutrition, COVID-19 Rehabilitation, COVID-19 Clinical manifestations, COVID-19 Risk factors and comorbidities, COVID-19 Vaccines, COVID-19 immunotherapy, COVID-19 Natural Killer Cells and stem cell therapy, COVID-19 Janus Kinase Inhibitor 1 and 2, COVID-19 air filtration, Nanomedicine for COVID-19, COVID-19 mental disorders, COVID-19 domestic abuse, COVID-19 Alzheimer's Disease and dementia, COVID-19 complications, COVID-19 Screening, COVID-19 ophthalmology, COVID-19 Neurological implications, COVID-19 antiviral, COVID-19 Steroids, COVID-19 Convalescent plasma, COVID-19 anticoagulants, COVID-19 monoclonal antibodies

INTRODUCTION

The report of the World Health Organization (WHO) states that the pandemic of SARS-CoV-2 has registered 15,785,641 confirmed cases globally and 640,016 deaths as of July 26, 2020 [1].

The first case of the Coronavirus Disease 2019 (COVID-19) was reported by Dr. Li Wenliang, an ophthalmologist in Wuhan China in December 2019. This respiratory disease presented similar symptoms to severe acute respiratory syndrome (SARS-CoV) in 2003. It was later named Severe Acute Respira-

tory Syndrome Coronavirus 2 (SARS-CoV-2) [2]. COVID-19 affects every age group; however, the elderly are more prone to a severe symptom display and have a higher mortality rate. Even with the majority of affected people being under the age of 65 (83.2%), people over the age of 65 still stands for 79.5% of all COVID-19 related deaths in the United States (US) [3]. An average of 13.3% of people over the age of 65 have a proven neurological comorbidity, including dementia [4]. Although the elderly population is most severely affected by the illness, a new study has found a higher SARS-CoV-2 viral RNA load in young children's nasopharynx than what had previously been found in older children (>5 years old) and adults [5]. Young children might therefore be far more likely to spread the virus than the anticipated asymptomatic spreaders. In other words, individuals of all age groups are prone to both contracting and spreading the virus, even when mild or no symptoms are present [6].

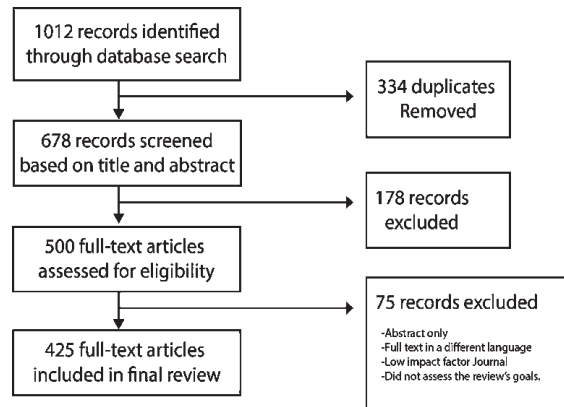
In recent months many papers have been published, criticized, discredited, and retracted. Thus, we believe this comprehensive review could update scientists about the state-of-the-science and technology and clarify any ambiguity about the current diagnostics and therapeutics strategies for COVID-19.

METHODOLOGY

As the COVID-19 pandemic surges worldwide, new information on the virus and its consequences are being published daily. We carried out a comprehensive review of available data to gather relevant information on the SARS-CoV-2 infection and organized it in a single article. Four primary investigators, VY, JB, JF, and SES, conducted searches for pertinent information published on the disease. In this paper, we focus on the virology, clinical features, risk factors and comorbidities, clinical manifestations, diagnosis, treatment, mental health, nutrition, rehabilitation, and general complications of COVID-19.

Search

Over 1,000 research articles, clinical studies, and news outlet sources with data and information about COVID-19 were assessed. Of the total number of articles, 425 individual records have been included in this review. No additional articles were retrieved after screening the references in both included reports and excluded reviews.



Databases used in the search for articles included PubMed, California Baptist University Library, ClinicalTrials.gov, Google Scholar, and multiple news sources. The search was restricted to articles about COVID-19 in English published between December 1, 2019 to August 4, 2020. We only considered articles for inclusion published in reputable journals with a high impact factor that pertained to the topic and investigational inquiries, as well as rigorous methodology.

Each article included was selected and reviewed by the 35 authors who then provided comments based on their area of expertise. Research papers were reviewed and critiqued independently; those not meeting the requirement for inclusion were excluded. Part of this data presented in this research paper is in development and not yet published, hence the need to convene a panel of COVID-19 treating specialists.

Keywords for the search included “COVID-19”, “Coronavirus”, “Novel Coronavirus Complications”, “COVID-19 Treatments, Epidemiology”, “SARS-CoV-2”, “COVID-19, mental health”, “COVID-19 neurology”, “ADRD”, “Alzheimer’s Disease”, “Long-term-care residents”, “COVID-19 renal”, “COVID-19 ophthalmology”, “COVID-19 rehabilitation”, “COVID-19 nutritional support”.

Articles on the origins of coronaviruses from the 1980s until the most recent ones were also included as additional background information for this article.

VIROLOGY OF COVID-19

Coronaviruses (CoVs) are enveloped, non-segmented, positive-sense, single-stranded, RNA viruses; belonging to the family *Coronaviridae*, broadly distributed in humans and other mammals [7].

Even though most coronavirus diseases are typically mild, two previous outbreaks in the past decades, SARS-CoV and the Middle East Respiratory Syndrome CoV (MERS-CoV), were severe. Collectively, SARS-CoV and MERS-CoV have produced more than ten thousand cumulative cases with a mortality rate of approximately 10% and 37%, respectively [7, 8].

The WHO recently classified SARS-CoV-2 as a β -Coronavirus, its genetic sequence displayed more than 80% similarity to SARS-CoV and 50% to MERS-CoV, both having their origins in bats [8]. Transmission since early on in the SARS-CoV-2 outbreak has been primarily from human-to-human, via direct contact or droplets expelled by sneezing or coughing from an infected individual at close range. Some fecal-oral transmission has been recognized [8, 13]. Prenatal infection of mothers has not shown to result in fetal or newborn infections [10, 11]. The mean reproductive number (R_0) based on clinical data of patients for COVID-19 was 2.24–3.58 [11], indicating that each infected individual, on average, would spread the disease to ~ 2 –3 other people [12, 13].

The virion of SARS-CoV-2 is approximately 50–200 nm in diameter [13]. It has at least four known structural proteins: spike (S) protein, envelope (E) protein, membrane (M) protein, and nucleocapsid (N) protein (see Fig. 1). All are required to assemble a complete viral particle. Recent studies have shown that some CoVs do not need all four proteins to be an infectious virion, suggesting that other

proteins with overlapping functionality may also be encoded [15].

The S protein is responsible for promoting host attachment and virus-target cell membrane fusion during virus infection [15, 16]. This protein has three segments that form a crown-like structure on the envelope, from which the family name derives: corona is Latin for crown [30]. The portions are constituted by a single-pass trans-membrane anchor, a short intracellular tail, and a large ectodomain, which consists of an S1 receptor-binding subunit S1 and a membrane-fusion subunit S2. The S1 portion binds to an ACE2 receptor and the serine protease TMPRSS2 on the host cell surface for viral attachment [29], the S2 portion mediates the fusion of the host and viral membranes, allowing viral genomes to enter host cells [17–19].

Earlier this year [20], the ACE2 receptor was recognized as the SARS-CoV-2 receptor, which is present in multiple human tissues, including type I and type II alveolar epithelial cells in the lung, in the gastrointestinal tract, in the basal cell layer of epidermis and hair follicles [21]. Also present at the cellular level in the central nervous system [22, 23], and in the kidneys and testes [24].

The SARS-CoV-2 S protein shares around 76% amino acids with the SARS-CoV and MERS protein [25], which may help explain its relatively high binding affinity to the human ACE2 receptor [23].

The N protein is attached to the CoV RNA genome and builds the nucleocapsid, which is part of the viral structure.

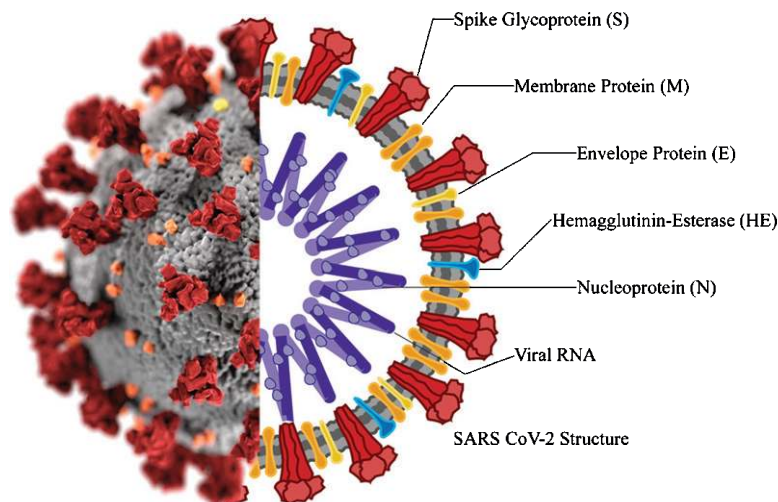


Fig. 1. Illustration of COVID-19 Structure. Adapted from the CDC images library [27] and Encyclopedia Britannica [28]. *Illustrated by Dr. Joe Bolanos.*

The M protein is the most abundant structural protein in the viral envelope. It interacts with all the major structural proteins in the CoV assembly process. The necessary interaction of S and M proteins maintains the S protein in the endoplasmic reticulum/Golgi complex for integration into new virions. The combination of the M and E protein consists to the structure of the viral envelope.

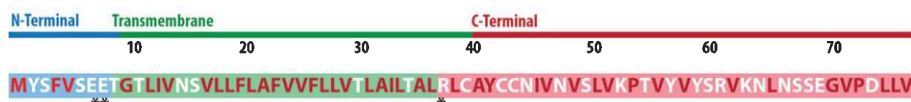
The E protein is the smallest of the structural proteins (containing 76–109 amino acids, in the range of 8.4 to 12 kDa in size), but it is the most important for viral replication [15]. During replication, the E protein is upregulated on the infected cell endoplasmic reticulum, and only a small quantity is incorporated into the new virion envelope. Studies have shown that recombinant CoVs that lack the E protein exhibit reduced viral titers and impaired viral maturation [15]. The CoV E protein has a short, hydrophilic amino terminus comprised of 7–12 amino acids. This is followed by a large hydrophobic transmembrane domain consists of 25 amino acids, and ending with an extended, hydrophilic carboxyl terminus that constitutes the majority of the protein. The transmembrane domain has two neutral amino acids: valine and leucine, that account for the E protein's hydrophobicity [26] (Fig. 2). The SARS-CoV E protein has a PDZ binding motif located in the last four amino acids of the C terminus. On co-immunoprecipitation and pull-down assays, the SARS-CoV E PDZ domain binds to PALS1 in mammalian cells, a tight junction-associated protein crucial for the establishment and maintenance of epithelial polarity in mammals [25]. Such functions and interactions exhibit multiple ways in which the E protein critically mediates SARS-CoV pathogenesis [25].

Analyses of 103 genetic populations of SARS-CoV-2 genomes showed that these viruses developed into two dominant strains, called L and S. The S type is the original strain and was less aggressive and less prevalent than L (30% versus 70% of cases, respectively). The L type strain was already more

frequent in the early stages of the Wuhan outbreak, but decreased in frequency after early January 2020 [31]. Later this year, further mutations were found, defining additional strains called A, B, and C [32]. Over time It is normal to collect random genomic mutations, which depend on age. Genomes develop variable mutations, constituting markers of disease spread. By building a phylogeny, it is possible to gather information about the epidemiological phenomena occurring to such pathogens, such as spread, their timeline of appearance and epidemic growth rate [33]. There are websites dedicated to tracking strains and updated daily, as the numbers of strains have increased [33]. Nextstrain.org identifies 5 major clades that correspond to GISAID nomenclature (in parenthesis): 19A (L) & (V), 19B (S), 20A (G), 20B (GR), 20C (GH). Different methods of classification and nomenclature are in place [34]. The GISAID initiative has classified the major SARS-CoV-2 clades and named them according to marker mutations in 6 major phylogenetic groups starting from the initial split of S and L, to the later division of L into V and G and later of G into GH and GR. So far 6 major clades have been identified based on 9 marker variants [34]:

- **S:** C8782T, T28144C includes NS8-L84S
- **L:** C241, C3037, A23403, C8782, G11083, G25563, G26144, T28144, G28882 (WIV04-reference sequence)
- **V:** G11083T, G26144T NSP6-L37F+NS3-G251
- **G:** C241T, C3037T, A23403G includes S-D614G
- **GH:** C241T, C3037T, A23403G, G25563T includes S-D614G+NS3-Q57H
- **GR:** C241T, C3037T, A23403G, G28882A includes S-D614G+N-G204R [34].

Based on the data available from GISAID the Geographical worldwide distribution of COVID-19 clades (GISAID) is illustrated in Fig. 3.



Amino Acid Sequence and Domains of the SARS-CoV E Protein. The SARS-CoV E protein consists of three domains, i.e. the Amino (N)-Terminal domain, the transmembrane domain (TMD), and the Carboxy (C)-Terminal domain. Amino acid properties are indicated: Hydrophobic (red), Hydrophilic (white) polar, charged (asterisks)

Fig. 2. Illustration SARS-CoV Protein E. Adapted from [15]. Illustrated by Dr. Joe Bolanos.

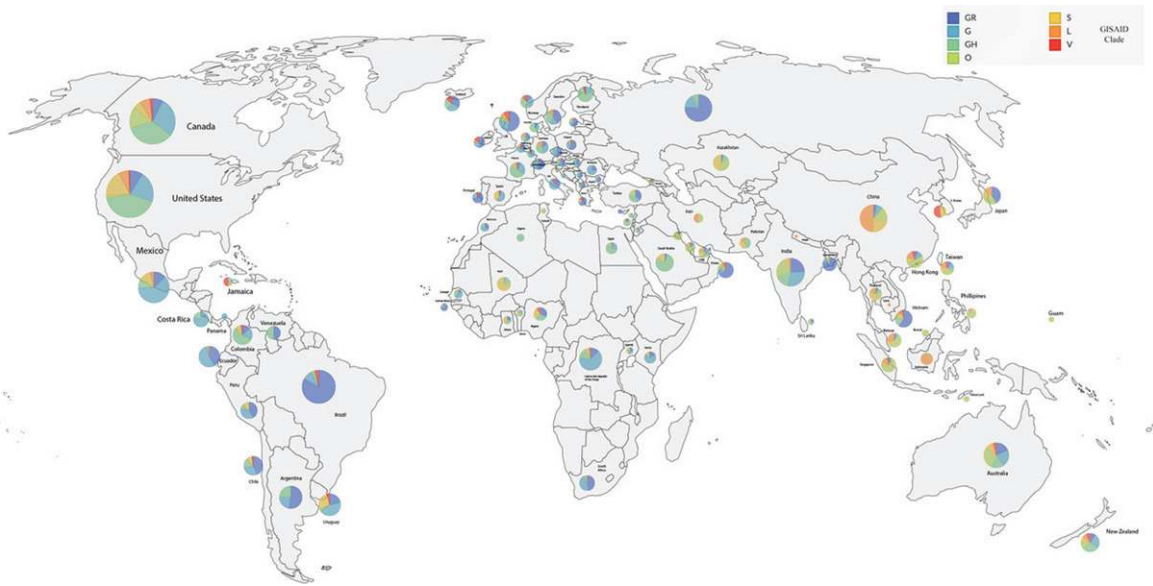


Fig. 3. Distribution of COVID-19 Worldwide distribution. Adapted from the GISAID Genomic Epidemiology of hCoV-19. Last updated 07-24-2020 https://nextstrain.org/ncov/global/gisaid?c=GISAID_clade&p=full [35]. Illustrated by Dr. Joe Bolanos.

CLINICAL FEATURES

Symptoms of the virus appear after an average of 5.2 days. The period between the onset of symptoms until death ranges from 6 to 41 days, which depending on the age, underlying health complications, level of care, and immune system status. The time from symptomatic onset to death is typically shorter in those over 70, median days (11.5 days) from the first symptom to death, than those with ages below 70 years (20 days) [8, 9].

The most common symptoms of COVID-19 in the US and China and most common laboratory findings of COVID-19 in China are shown in Fig. 4 [31, 43–45]. The Centers for Disease Control and Prevention (CDC) lists additional COVID-19 symptoms reported, including anosmia, ageusia, sore throat, and muscle pain [36], skin rashes and acro-ischemic lesions of the feet (anecdotally called “COVID toes”) and hands are reported [37–39]. Children tend to exhibit milder symptoms than adults [40–42].

Risk factors and comorbidities

Studies have revealed how patients who develop SARS- CoV-2 pneumonia also tended to have underlying medical conditions such as hypertension (12.8–30%), diabetes (5.3–12.1%), and cardiovascular disease (4.2%) [46, 47]. Patients exhibiting severe

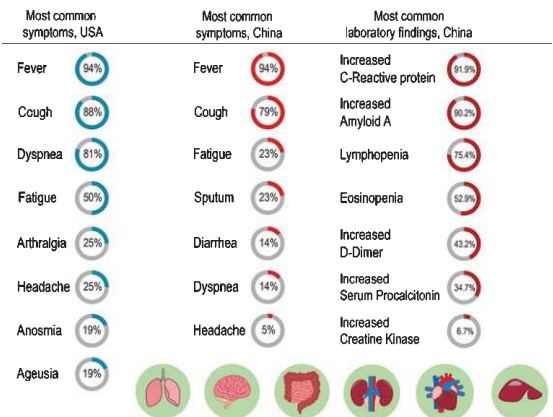


Fig. 4. Most common COVID-19 symptoms in US and China. Most common laboratory findings in COVID-19 in China [31, 43–45]. Illustrated by Dr. Joe Bolanos.

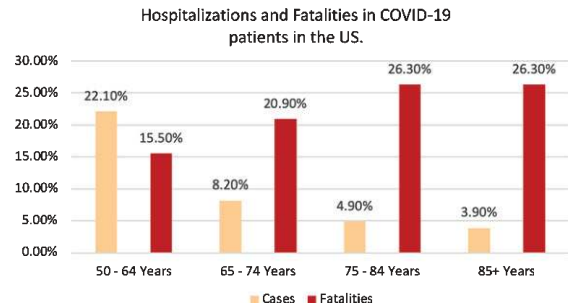
COVID-19 admitted to the intensive care unit (ICU) showed a greater tendency toward such comorbidities [46, 47]. There are additional reports of comorbidities with lower frequencies.

The age group with the most cases was the sixth decade of life, followed by seventh decade, and then the fifth decade of life group [43]. Accordingly, hospitalization for patients in the seventh, eighth, and ninth decade of life are 11.8%, 16.6%, and 18.4%, respectively [43]. The groups with the most fatalities are the ninth, eighth, and seventh decades of life groups

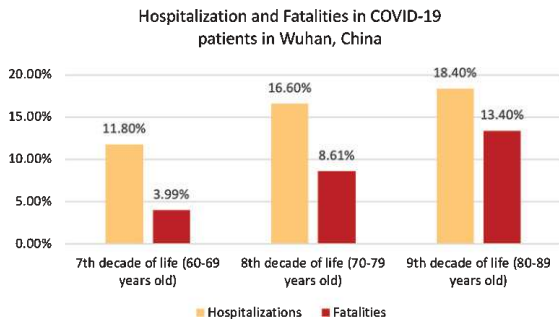
(shown in Graph 1). According to the CDC, as of July 2020, there have been 3,186,778 positive cases in the US. The largest age group presenting COVID-19 cases is the 50–64 years old group (22.10%), followed by the 65–74 years old (8.20%), 75–84 years old (4.9%), and 85+ years old (3.9%). Fatalities, however, show a different trend as illustrated in Graph 2.

Clinical manifestations

The clinical manifestations of COVID-19 range from asymptomatic or mild disease, to respiratory failure requiring mechanical ventilation and intensive care unit support, to widespread multi-organ-systemic disease [48]. Acute respiratory distress



Graph 2. Hospitalizations and Fatalities in COVID-19 patients in the US [3].



Graph 1. Hospitalizations and Fatalities in COVID-19 patients in Wuhan, China [43].

syndrome (ARDS) trend prevalence is higher in the older age group, while a more significant percentile of heart, liver, and kidney function injuries were seen in the younger group [49]. Clinical presentation of patients with COVID-19 includes severe dyspnea and hypoxemia, renal impairment with decreased urine output, tachycardia, altered mental status, and multiple organ dysfunction. This clinical presentation is accompanied by altered laboratory values such as hyperbilirubinemia, acidosis, high lactate, coagulopathy, and thrombocytopenia [50].

The Chinese Center for Disease Control report has classified the disease by severity (see Table 1).

The Chinese guidelines for diagnosis and treatment of SARS-CoV-2 infection classify pneumonia caused by the novel coronavirus 2019 in four types. See Table 2 [48, 50].

Table 1
Adapted from [48] Classification of COVID-19 Pneumonia like symptoms

Mild	Non-pneumonia and mild-pneumonia in approx. 81% of cases [48].
Severe	Dyspnea, Respiratory Rate ≥ 30 rpm, blood oxygen saturation (SpO ₂) $\leq 93\%$, PaO ₂ /FiO ₂ ratio or P/F < 300, and/or lung infiltrates >50% within 24 to 48 hours. 14% of cases [48].
Critical	Respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF), which occurred in 5% of cases [48].

Table 2
Adapted from [48, 50] Classification of severity of COVID-19

Mild	Usually presenting symptoms of an upper respiratory infection: mild fever, dry cough, sore throat, nasal congestion, malaise, and headache, but no imaging signs of pneumonia [48, 50].
Moderate	Presenting respiratory symptoms, such as cough and dyspnea (tachypnea in children), and imaging signs of pneumonia [48, 50].
Severe	Presents with any of the following: <ul style="list-style-type: none"> – Fever – Severe dyspnea, respiratory distress, and tachypnea with RR > 30 rpm – Hypoxia < 90%, or PaO₂/FiO₂ < 300 mmHg. – Cyanosis could be present in children [48, 50]
Critically Severe	– Respiratory failure needing mechanical ventilation [48, 50]

Ocular involvement

Exposed ocular surfaces are vulnerable to infection by droplets as are other mucous membranes [51]. According to a study in 38 patients, in Hubei, 12 presented ocular symptoms. Ophthalmic manifestations from COVID-19 ranged from conjunctival hyperemia (3 patients), follicular conjunctivitis, chemosis (7 patients), and epiphora (7 patients) [52] to hyper-reflective lesions in the ganglion cell and inner plexiform layers of the retina (12 patients, as reported in a study in Sao Paulo) as shown by optical coherence tomography [53]. COVID-19 hypercoagulable states have been correlated with blindness, due to acute ophthalmic artery occlusion [54].

The ocular surface could facilitate the virus to reach the nasopharynx through the nasolacrimal system [55]. Tears have been shown to harbor SARS-CoV-2 thus every healthcare worker needs to take caution as 7% of COVID-19 patients may present the virus in their tears, but be asymptomatic [56] and while studies have shown positive SARS-CoV-2 RT-PCR results from a patient's tears, virus isolation remains difficult [57].

Neurological implications

Human coronaviruses (HCoVs), and other respiratory viruses may enter the central nervous system (CNS) hematogenously or by the ethmoidal cribriform plate by retrograde neuronal route [23, 58]. COVID-19 as a subject infects the blood-brain-barrier's endothelial cells and the blood-cerebrospinal fluid barrier's epithelial cells in the choroid plexus brain's ventricles, or leukocytes that become hematogenous propagation vectors [58].

The critical role of proteins S and E in HCoVs, specifically OC43, and the slow movement of the blood in the brain's microcirculation, can aid in the interaction of the SARS-CoV-2 S protein with the ACE2 receptor expressed in the capillary endothelium. Viral damage and recruitment of endothelial cells can promote invasion of the CNS by SARS-CoV-2 [23, 59–62].

In the retrograde neuronal route, infection occurs in the body's periphery and axonal transport mechanisms are used to access the CNS [63, 64]. Respiratory viruses use the olfactory, trigeminal, and vagus cranial nerves to access the brain [65–72].

The four endemic HCoVs have associations with extra-respiratory diseases such as myocarditis, meningitis, severe diarrhea, and multi-organ failure [73–78]. There have been reports linking the presence of HCoVs in the human CNS and neuro-

logical disorders [79–83]. Identifying the etiology of CNS infections poses a challenge. These difficulties arise due to the spectrum of symptoms that infected patients present and the number of pathogens that can cause them. It is also challenging to differentiate a non-viral etiology from systemic viral infection's symptoms outside of the CNS [84–87].

CNS infections can present as meningitis with fever, neck stiffness, photophobia, and phonophobia. Encephalitis' symptoms may be mild and undiagnosed or attributed to other system's imbalances. Typical encephalitic symptoms such as confusion, altered mental status, personality change, abnormal behavior, movement disorders, and seizures have also been reported [84].

In a case series, in which autopsies were performed and brain specimens collected, histopathological studies showed only hypoxic changes without evidence of viral encephalitis in SARS-CoV-2- exposed patients [88]. However, in a study that involved 153 hospitalized patients, clinical data were available for only 125, which showed that the most common presenting neurological or psychiatric disorder was a cerebrovascular episode in 62% of patients, followed by altered mental status in 31% of patients. The altered mental status' etiology, ranged from encephalopathy (nine patients) to encephalitis (seven patients). The remaining 59% exhibited psychiatric conditions, such as neurocognitive syndrome, psychosis, and affective disorders. Only two patients had exacerbations of pre-existing mental disorders. About 50% of patients with altered mental status were younger than 60 years of age, while 82% of patients with cerebrovascular episodes were over 60 years of age [89].

In 214 hospitalized COVID-19 patients in Wuhan, 36.4% of patients with mild disease had neurological symptoms, and 45.5% presented them, when severely compromised [90]. Symptoms exhibited are seen in Table 3.

A review of literature has shown COVID-19 to be linked with a high number of cases of ageusia and anosmia. It is due to the entry of the COVID-19 virus through the nasal epithelium, which includes respiratory epithelium and olfactory epithelium [91].

Many viruses, including coronaviruses, do induce brief fluctuations in odor acuity due to different inflammatory responses, including cytokine release. Other β -coronaviruses often lead to inflammation, while SARS-CoV-2 does not cause nasal epithelium inflammation. The anosmia caused due to SARS-Cov-2 usually takes weeks for recovery. In contrast,

Table 3
Neurological Symptoms of COVID-19 [90]

CNS = 24.8%		PNS = 8.9%		Skeletal muscle	
Dizziness	16.80%	Smell impairment	5.6%	Skeletal muscle injury	10.7%
Headache	13.1%	Taste impairment	5.1%		
Altered Consciousness	7.5%	Nerve pain	2.3%		
Acute cerebrovascular disease	2.8%	Vision impairment	1.4%		
Ataxia	5.0%				
Seizures	5.0%				

CNS, central nervous system; PNS, peripheral nervous system.

conventional post-viral anosmia is linked to the immediate destruction of olfactory sensory neurons and can take several months for recovery [91].

A study has shown that the identification of non-neuronal cell types in the olfactory epithelium makes patients affected with SARS-CoV-2 highly vulnerable and cause anosmia [91].

Anosmia and ageusia are associated with COVID-19 [92, 107]. In a study of 417 European patients, 357 (85.6%) presented viral-associated olfactory dysfunction. 79.6% presented anosmia, while 20.4% presented hyposmia. Phantosmia and parosmia represented 12.6% and 32.4%, respectively. Most (65.4%) presented olfactory dysfunction after the onset of otorhinolaryngologic symptoms, 22.8% presented both at the same time, while only 11.8% before symptom onset. 63% of all were asymptomatic, but presented olfactory dysfunction persistence [92].

In a French study of 58 COVID-19 patients with ARDS, neurologic features were observed in 49 patients, including prominent agitation, confusion, and corticospinal tract signs [93]. COVID-19 positive patients with strokes have been reported worldwide, and numbers are increasing [94, 98–101]. The virus has not been detected in the cerebrospinal fluid, despite being positive on a COVID-19 nasal swab via RT-PCR. SARS-CoV-2's isolation in the cerebrospinal fluid may be dependent on the disease being systemic or not [102–105]. Further studies will be required to determine if the neurological symptoms are caused by the virus itself or indirectly by secondary, infectious, systemic inflammatory responses. Magnetic resonance imaging (MRI) in the early phase of infection in patients with anosmia, cerebrospinal fluid testing and pathology studies would be helpful to document objective radiological data [106].

While most neurological manifestations have been non-focal, some cases of severe and critical COVID-19 have been shown to present with strokes [93].

As per Mao et al., the rate of neurovascular events in their series was about 5.7% of which about 4.9% had ischemic strokes [88]. Most ischemic strokes in these case series were subcortical or distal emboli. Some cases were related to other risk factors like atrial fibrillation, diabetes, or hypertension. Other cases, coagulation pathway disorders directly associated with the viral inflammation or immunological response, like antiphospholipid antibodies or elevation of D-dimer and Fibrinogen, may have been responsible [93].

No specific correlation with COVID-19 associated strokes and age or pre-stroke severity of the disease has been found [94]. All the cases had a high neutrophil-lymphocyte ratio except for one. Almost half of the patients who were part of this cohort presented with large vessel occlusions. Eighty percent of those underwent a thrombectomy, most of them having poor outcomes, and this was typically secondary to non-neurological aspects of the disease such as ARDS or multiorgan failure [94]. COVID-19 related ischemic events can follow multiple etiopathogeneses. Hypertension, however, has not been independently associated with severity of COVID-19 [95]. Finally, paradoxical emboli from venous thromboembolism are yet another confounding cause of ischemic events in the brain [96, 97].

DIAGNOSIS

Laboratory diagnostic methods have proven to be reliable in diagnosing COVID-19 and have been presented in tabular form in Table 4 [48, 108].

TREATMENT

The primary treatment for COVID-19 is symptomatic, if mild. The universal treatment used in patients with moderate, severe, or critical presenta-

Table 4

Laboratory, Imaging, RT-PCR, and Antigen test common and severe findings. Adapted from [2, 48, 108, 109, 113–116, 118]

	Early stage of infection/Common findings	Late stage/severe cases of infection/severe findings
Laboratory findings	Lymphopenia, elevated AST, LDH, muscle enzymes [108], CRP, and ESR [48]. Procalcitonin values are normal [48, 109].	Elevated D-dimer, reduced lymphocyte counts with altered laboratory values indicating multi-organ failure. High levels of ALT and AST [48, 108, 109, 113]. IL-6 induces gene expression and the release of CRP [114]. IL-6 is part of the host defense mechanism to combat infections and tissue injuries. When expressed excessively while fighting SARS-CoV-2, it can trigger a severe acute systemic inflammatory response, cytokine storm [115]. Studies have shown that serum levels of IL-6 and CRP can evaluate severity of disease, predict the need for mechanical ventilation and estimate prognosis in COVID-19 patients [114–116].
Imaging studies	Bilateral, diffuse, patchy ground-glass opacities with or without consolidations in a peripheral, posterior, or lower lung zone distribution [108, 109]. Studies revealed that a slight majority of patients had a negative CT during the first two days of symptom onset, with a ground-glass opacity usually developing between day 0 and 4 after the beginning of symptoms, and peaking between day 6–13 [110].	Lymphadenopathy and pleural effusion have been reported more rarely. Other studies report that the sensitivity of chest CT to reflect SARS-CoV-2 infection in suspected patients accurately, was 97% based on RT-PCR positivity, and 75% based on negative RT-PCR results. These findings showed that chest CT is a sensitive test to confirm SARS-CoV-2 infection in conjunction with RT-PCR [2].
A negative CT should not be used to exclude the possibility of COVID-19 infection in its early stages. On the contrary, the use of CT is recommended in clinical management and screening of incidental findings that are potentially attributable to COVID-19 [110]. Available data regarding these CT findings are limited, such that new patterns may emerge with further studies [112]. Some studies suggest that over 20% of patients with COVID-19 may have coexistent infections, which can obscure the relationship of CT findings to the disease process [110].		
RT-PCR	Main clinical laboratory diagnostic test in COVID-19 detection [2]. RT-PCR from a respiratory specimen is currently the most accurate test to screen and diagnose an active COVID-19 infection. Not all tests are equivalent, however, and as such their acceptance on approved test lists is critically important [110]. The CDC recommends the collection and testing of an upper respiratory specimen, with nasopharyngeal being the preferred route. An oropharyngeal sample, nasal mid-turbinate swab, and an anterior nares specimen are acceptable alternatives when the sampling of a nasopharyngeal swab is not possible.	For patients receiving invasive mechanical ventilation, a lower respiratory tract aspirate or bronco-alveolar lavage sample should be collected and tested [112]. The sample requires storage at 2–8°C for up to 72 h after collection. If testing or shipping is delayed, the specimen should be stored at –70°C or lower [112, 117]. The positive rate of RT-PCR for throat swab samples in early stages of COVID-19 has been unacceptably low at 60% [118]. In a study of 51 patients, the positivity rate for a single respiratory swab was still just 70%, but adding a second test elevates this to 94%, and a third test increasing that to 98% [118]. Thus, at least two and if possible three, independent RT-PCR analyses are recommended to confirm COVID-19 diagnosis.
Antigen testing	COVID-19 IgM/IgG rapid testing using blood samples revealed a reduced sensitivity in detecting infection, and often less than 20%. The majority of patients testing positive for COVID-19 by RT-PCR would have tested negative using the rapid serological assay alone, highlighting the potential for misdiagnosis of COVID-19 using the latter assay in isolation [110, 111]. The rapid antigen tests are thus not recommended for screening active COVID-19 infections but rather for monitoring those exposed to COVID-19 previously, and regardless of recovery.	

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CRP, C-Reactive protein; CT, computed tomography; ESR, Erythrocyte sedimentation rate; LDH, lactate dehydrogenase; RT-PCR, Reverse transcription-polymerase chain reaction.

tions is supportive care. In patients presenting with hypoxia or respiratory failure, despite supplemental oxygenation and worsening dyspnea, the use of mechanical ventilation should be considered. Extracorporeal membrane oxygenation should be used as a last resort [2, 7, 14], identifying specific clinical characteristics of critical COVID-19 patients may improve outcome [119].

Mechanical ventilation

Mechanical ventilation is recommended with lower than normal tidal volumes (4 to 6 ml/kg predicted body weight) and lower inspiratory pressures, reaching a plateau pressure <28 to 30 cm H₂O. The positive end-expiratory pressure (PEEP) must be high to maintain the driving pressure (P_{plat}-PEEP)

low <14 cm H₂O [48]. Avoiding ventilator disconnections is critical to prevent atelectasis and loss of PEEP. Paralytics inducers should be used only if PaO₂/FiO₂ < 150 mmHg. Prone ventilation lasting longer than 12 hours a day, and conservative fluid management (ARDS strategy in patients without hypoperfusion) are strongly recommended [48, 123].

Antivirals

Oseltamivir (75 mg BID every 12 hours PO, orally), Ganciclovir (250 mg BID every 12 hours IV, intravenously) ribavirin, Lopinavir/Ritonavir tablets (400/100 mg BID every 12 hours PO, orally) [48] have all been used in efforts to decrease viral load, and to avoid the probability of respiratory complications in several studies [2, 7, 12–14].

Remdesivir, a broad spectrum antiviral [124] that inhibits RNA dependent RNA- polymerase, was successful in the control of *in vitro* SARS-CoV-2 [12, 125, 126], and it is hypothesized that it could be efficacious for prophylaxis and therapy of human coronavirus infections [48]. The first dosage under investigation for treatment of COVID-19 was 200 mg intravenously (IV) on day 1 followed by 100 mg IV daily for up to 10 days, infused over 30–60 minutes [127]. More recent studies have demonstrated there is no clinical difference between the administration of the same dosage for 5 or 10 days [128].

Steroids

The WHO report results from a clinical trial in the United Kingdom where the use of dexamethasone showed promising, lifesaving results for critically ill COVID-19 patients. In the study, preliminary findings showed that mortality was reduced by one-third for patients on ventilators, and one-fifth for patients on oxygen [120].

Anticoagulants

COVID-19 can induce an immune-thrombotic and disseminated intravascular coagulation, which can explain for thrombosis on a consumptive basis [121]; however, the thrombotic effects of COVID-19 are not completely understood [122].

A non-randomized retrospective study of 351 patients evaluated preemptive administration of prophylactic anticoagulants versus therapeutic anticoagulants. The average age of the participants in

the study was 64.7 years old, with a distribution of 58.6% male and 41.4% female. A 93.5% of the sample group were on enoxaparin, 14.8% on heparin, and some were on both medications. The results showed a difference in in-hospital mortality among COVID-19 patients and those with significantly elevated C-Reactive protein (CRP) levels (>200 mg/L) [122]. The most common causes of death between patients were refractory acute respiratory failure with hypoxia, shock, and multi-organ system failure. Thrombosis could point the etiology of death, but it could also be attributed to direct viral end-organ damage or to a viral systemic inflammatory response syndrome. The study showed no prevention in the progression of disease with a therapeutic dosage of anticoagulation [122].

The risk of mortality was 2.3-fold higher for patients on therapeutic anticoagulants compared to the ones just taking them prophylactically, after controlling other variables. Even for patients with elevated CRP levels, there was no clinical improvement in administering preemptive therapeutic anticoagulation. The study recommends considering the risks and benefits for the patient, as well as a cautious approach in the use of anticoagulation in the management of COVID-19 patients who require them [122].

Convalescent plasma

In an uncontrolled study of 5 critically ill patients with COVID-19, who were receiving mechanical ventilation, antivirals, and methylprednisolone with an age range of 36–65 years old, the use of convalescent plasma containing neutralizing antibody resulted in clinical improvement of symptoms, ARDS resolution, and weaning of mechanical ventilation, with an increase in the levels of SARS-CoV-2 antibodies [129].

Monoclonal antibodies

Specific neutralizing monoclonal antibodies, either against receptor-binding domain of spike protein or those binding to ACE2, could effectively block SARS-CoV-2 virus entry. Several monoclonal antibodies have yielded promising results in neutralizing SARS-CoV and MERS-CoV *in vitro* or *in vivo* [130].

Anti-malarial

The combination of Hydroxychloroquine (HCQ) (600 mg/day)/Azithromycin (500 mg/day) has been

used in the treatment against SARS-CoV-2's COVID-19 [131]. Both Chloroquine (CQ) and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes and lysosomes that are essential for membrane fusion. It was hypothesized that CQ could inhibit SARS-CoV entry by changing the glycosylation of the ACE2 receptor and spike protein [132].

More recently, a multinational observational, real-world study of hospitalized patients with COVID-19 showed that the use of a regimen containing HCQ or CQ with or without a macrolide was linked with no benefit, but instead associated with an increase in the risk of ventricular arrhythmias and a higher risk for in-hospital death with COVID-19 [133]; however, this study was retracted by the journal that published it, because there were concerns regarding the veracity of the data and analyses conducted by the authors and the database's rights holding corporation [134].

A multi-hospital, retrospective cohort study evaluating clinical outcomes at the Henry Ford Health System in Michigan found that when controlling for COVID-19 risk factors, the treatment with HCQ or HCQ with azithromycin, was associated with reduction of mortality in COVID-19 patients [135]. So far, the information regarding these drugs has been mixed and inconclusive.

The potential treatment for COVID-19/SARS-CoV-2 and the mechanisms of action of the various medications at the cellular level including Fusion and endocytosis, translation, proteolysis, RNA Replication to Packaging can be seen as illustrated in Fig. 5.

Vaccines: Traditional protein targets

There is no FDA approved COVID-19 vaccine available to date. Even with the use of novel platforms, developing a vaccine for SARS-CoV-2 poses a challenge. The optimum design of the immunogen based on viral protein S, the existing adverse effects in vaccines exacerbating lung disease and the uncertainty of whether these new single-dose vaccines will confer immunity and for how long, have yet to be established. Vaccine development is a lengthy and costly process that commonly involves several vaccine candidates and years for approval [48, 136, 145, 147].

The development of a protein subunit vaccine for COVID-19 using microneedle array to deliver MERS-S1 subunits to induce long-lasting

potent immunogenicity is underway. Past studies on adenoviral vaccines expressing SARS-CoV-1 and MERS-S1 subunits demonstrated a more robust antibody-antigen neutralizing activity than when using "S1" alone [136].

The uncertain status of a SARS-CoV-2 vaccine has promoted interest in natural herd immunity to the virus. Herd immunity is the state when a large enough proportion of a population has achieved protective immunity against a pathogen to limit its spread among non-immune individuals critically. It requires protective immunity in 50–90% of the population, and may be acquired through natural exposure, hence many dangerous pathogens require vaccination to achieve and sustain it [137]. An additional concern with SARS-CoV-2, is that natural exposure may not confer protective immunity to all individuals, as reinfection after initial exposure and evidence of immunosuppression have both been reported [7, 138, 139]. In the case of SARS-CoV-2, it cannot be naturally achieved without dire public health consequences. Assuming protective immunity is required in just 70% of the US population (328M), and given infection rates as high as 10–20%, the unrealistic development of immunity in 100% of those infected [140, 141], and mortality as low as 1%, a minimum of 300,000–500,000 COVID-19 deaths can be expected over 7.5–13 months before the US achieved natural herd immunity [142, 143]. While these views are popular, they clash with current knowledge of SARS-CoV-2 infection, mortality, and immune dynamics [144].

The current vaccine development techniques for COVID-19 can be seen in Table 5. Table 6 present a list of vaccines that have been approved for clinical testing along with the different phases they are in currently. Table 7 presents a list of treatment options in development for COVID-19.

Natural killer cells and stem cell therapy

Natural killer (NK) cells are part of the human innate immunologic system that destroys the virally infected or neoplastic cells. COVID-19 infected patients present a significant decrease of total lymphocytes, CD4-T/CD8-T cells or B cells and NK cells [146].

The purpose of the therapy with NK cells infusion is to benefit those patients with new onset of symptoms or those who have a high risk for severe disease, due to cytokine storm [148]. The infusion of NK cells, derived from placental stem cells, boosts the immune

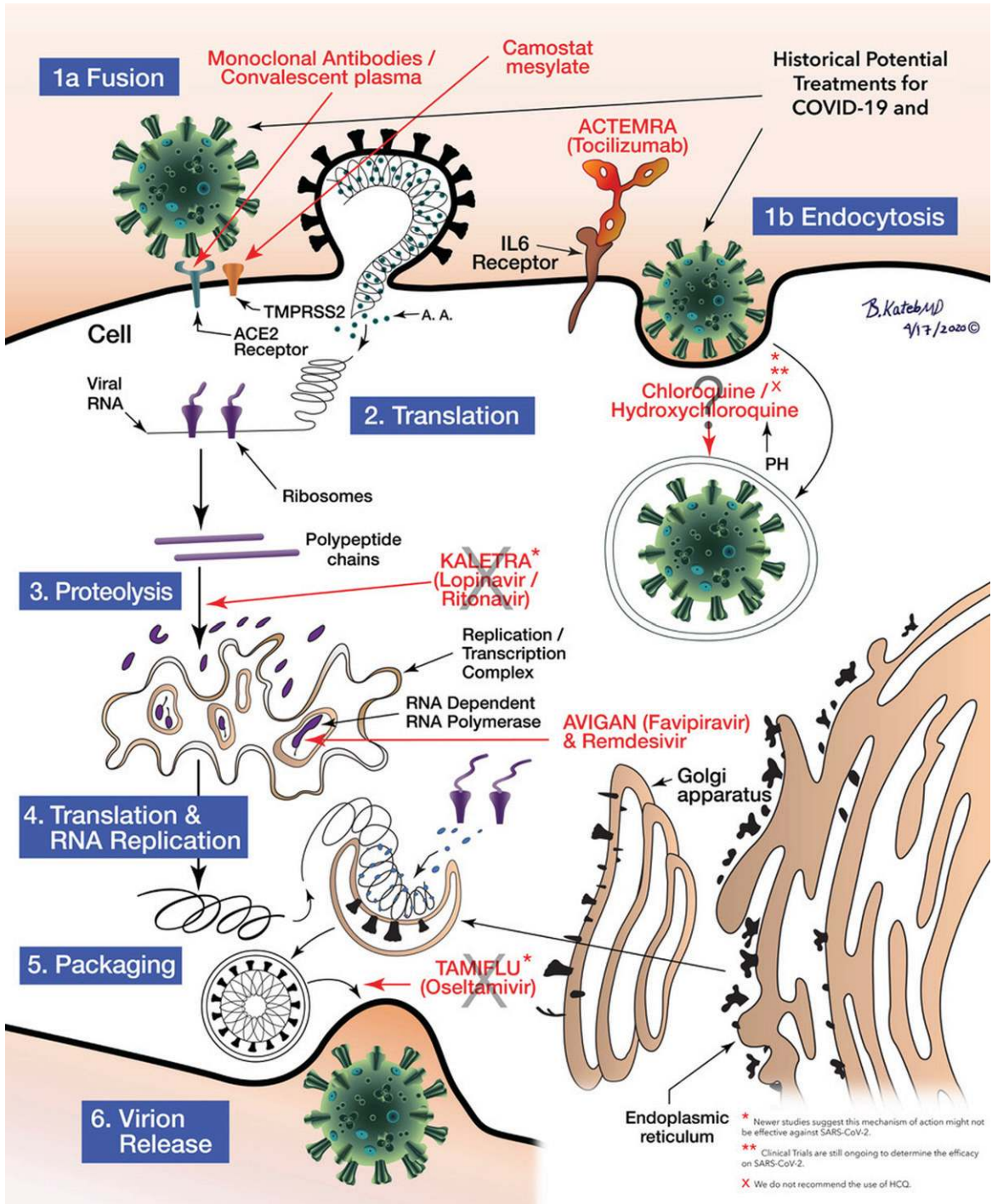


Fig. 5. Schematic illustration of anti COVID-19 medications' mechanisms of action. *Illustrated by Dr. Babak Kateb.*

response against COVID-19 infected cells, limiting SARS-CoV-2 replication and disease progression by eliminating the infected cells. This option is in the clinical trial phase [148–150].

Mesenchymal stem cells (MSCs) are being used in clinical trials. In one of the studies, two days post-transplantation of MSCs, there was a noticeable improvement of pulmonary functions and symptoms.

Table 5
 COVID-19 Current Vaccine Development Techniques. Adapted from [145]

COVID-19 Vaccines Techniques							
Attenuation	Inactivation	Fractionation		Cloning		Expression	
Codagenix/ SII	SinoVac/ Dynavax	Non-recombinant purified purified subunit		Cloning		Protein	
				Replication competent virus vector vaccine	DNA Vaccine		
		Clover Bio- pharm/GSK	Novavax	Tonix Pharma/Southern Research	Inovio/Beijing	Virus-Like Particle vaccine	Subunit Vaccine
		Baylor/UTMB/ NYBC/Fudan	Vaxart	Altimune	Advaccine	Geovax labs/Bravovax	Clover Biopharm/ GSK
		UQ/GSK/ Dynavax	Generex	Greffex	Biotech	Medicago	Baylor/UTMB/ NYBC/Fudan
		Generex/ EpiVax	ExpreS2ion	Vaxart	Applied DNA Sciences		UQ/GSK/ Dynavax
		Sanofi Pasteur	Vaxil Bio	Zyus	Takis Biotech/Evvivax		Generex/ EpiVax
		Walter Reed/ USAMRIID	EpiVax/ Ugeorgia	Cadla	Zyus Cadila		Sanofi Pasteur
		iBio/CC- Pharming		Institute Pasteur			Walter Reed/ USAMRIID
				Non- replicating viral vectors	RNA Vaccine		iBio/CC- Pharming
				CanSino (Ad5)	Moderna/NIAID		Novavax
				J&J/BARDA (Ad26)	CureVac		Vaxart
				Univ. Oxford (ChAdOx1)	Arcturus/Duke/NUS		Generex
					BioNTech/Pfizer		ExpreS2ion Vaxil Bio EpiVax/ Ugeorgia

The laboratory findings showed an increase in peripheral lymphocytes, a decrease in CRP, the complete resolution of the overactivated cytokine secreting immune cells like CD4 + T-cells, CD8 + T-cells, and NK cells, a reduction in TNF- α , and an increase in IL-10.

The intravenous infusion of MSCs looks to be a safe alternative for treating patients with severe cases of COVID-19. Despite this data, further studies in a more significant population cohort are needed to corroborate this therapeutic intervention [151].

A study demonstrated the presence of S- reactive CD4 + T cells in COVID-19 patients and also in unexposed healthy individuals. These pre-existing S-reactive T-cells could be cross-reactive clones obtained in prior infections with endemic HCoV's that account for ~20% of the yearly common cold.

The function of the pre-existing S-cross-reactive CD4 + T-cells in 35% of the healthy individuals is

still unknown; however, if these cells are protective in a SARS-CoV-2 infection, they could provide some understanding in the different manifestations of COVID-19, and shed some light in why children and young adults appear to be more resistant to symptomatic SARS-CoV-2 infection [152].

Allogeneic cardiosphere-derived cells

In a series of non-randomized cases of 6 COVID-19 positive patients, with an age range of 19–75 years, cardiosphere-derived cells (CDCs) were used to treat patients who were positive for and exhibited lung injury. CDC's mechanism of action is to target several cytokine pathways (e.g., IL-1, IL-6, TNF α), which levels decreased after the infusion. All patients showed clinical recovery and were extubated [153].

Table 6
Ongoing clinical trials for COVID-19 vaccines [212–239]

Vaccine	Company	Platform	Phase/Status	Primary purpose	Trial description	Location
BCG Vaccine [212]	Texas A&M University	Live attenuated	IV Recruiting	Prevention	A randomized, parallel assignment trial N = 1800, health care workers (HCW) Study start date: April 20, 2020	USA
BCG Vaccine [213]	Hellenic Institute for the Study of Sepsis	Live attenuated	IV Recruiting	Prevention	A randomized, parallel assignment trial N = 900 Study start date: May 26, 2020	Greece
BCG Vaccine [214]	Murdoch Children's Research Institute	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 4170, HCW Study start date: March 30, 2020	Australia
BCG Vaccine [215]	UMC Utrecht	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 1500, HCW Study start date: March 25, 2020	Netherlands
BCG Vaccine [216]	TASK Applied Science	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 500, HCW Study start date: April 28, 2020	South Africa
VPM1002 [217]	Vakzine Projekt Management GmbH	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 1200, HCW Study start date: May 25, 2020	Germany
VPM1002 [218]	Vakzine Projekt Management GmbH	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 2038, people over 60 y/o Estimated study start date: June, 2020	Germany
MMR vaccine [219]	Kasr El Aini Hospital	Live attenuated	III Recruiting	Prevention	A randomized, parallel assignment trial N = 200, HCW Study start date: June 16, 2020	Turkey
ChAdOx1 nCoV-19 [220]	University of Oxford	Non-Replicating Viral Vector	II/III Recruiting	Prevention	A randomized, sequential assignment trial N = 10260 Study start date: May 28, 2020	UK
Ad5-nCoV [221]	Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China/CanSino Bio. Inc.	Non-Replicating Viral Vector	II Active, not recruiting	Prevention	A randomized, crossover assignment for evaluation of Ad5-nCov, which encodes for full-length S-protein of SARS-CoV-2. N = 500 Study start date: April 12, 2020	China
mRNA-1273 [222]	ModernaTX, Inc.	RNA	II Recruiting	Prevention	A non-randomized, sequential assignment trial N = 600 Study start date: May 29, 2020	USA
Inactivated SARS-CoV-2 Vaccine [223]	Sinovac/Development Co., Ltd.	Inactivated	I/II Recruiting	Prevention	A randomized, parallel assignment trial for the prevention of the COVID-19 disease N = 744 Study start date: April 16, 2020	China

(Continued)

Table 6
(Continued)

Vaccine	Company	Platform	Phase/Status	Primary purpose	Trial description	Location
Inactivated SARS-CoV-2 vaccine (Vero cells) [224]	Beijing Institute of Biological Products/Sinopharm	Inactivated	I/II Recruiting	Prevention	A randomized, double-blind trial N = 21 Study start date: April 28, 2020	China
Inactivated SARS-CoV-2 vaccine [225]	Chinese Academy of Medical Sciences	Inactivated	I/II Recruiting	Prevention	A randomized, parallel assignment, quadruple trial N = 942 Study start date: May 15, 2020	China
Gam-COVID-Vac [226]	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Non-Replicating Viral Vector	I/II Recruiting	Prevention	A non-randomized, parallel assignment, quadruple trial N = 38 Study start date: June 17, 2020	Russia
Gam-COVID-Vac Lyo [227]	Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	Non-Replicating Viral Vector	I/II Recruiting	Prevention	A non-randomized, parallel assignment, quadruple trial N = 38 Study start date: May 15, 2020	Russia
GX-19 [228]	Genexine, Inc.	DNA	I/II Recruiting	Prevention	A randomized, parallel assignment, quadruple masked trial N = 190 Study start date: June 17, 2020	Republic of Korea
Inactivated Vaccine [229]	Beijing Institute of Biological Products/Sinopharm	Inactivated	I/II Recruiting	Prevention	A randomized, parallel assignment trial N = 1448 Study start date: April 11, 2020	China
INO-4800 [230]	Inovio Pharmaceuticals	DNA	I Recruiting	Prevention	A non-randomized, sequential assignment trial N = 40 Study start date: April 3, 2020	USA
NVX-CoV2373 [231]	Novavax	Protein Subunit	I Recruiting	Prevention	A randomized, parallel assignment, triple masked trial N = 131 Study start date: May 25, 2020	Australia
mRNA-1273 [232]	National Institute of Allergy and Infectious Diseases (NIAID)	RNA	I Recruiting	Prevention	A non-randomized, sequential assignment trial N = 155 Study start date: March 16, 2020	USA

CVnCoV [233]	CureVac AG	RNA	I Recruiting	Prevention	A randomized, sequential assignment, single masked trial N = 168 Study start date: June 18, 2020	Belgium/ Germany
SCB-2019 [234]	Clover Biopharmaceuticals AUS Pty Ltd	Protein Subunit	I Recruiting	Prevention	A randomized, sequential assignment, triple masked trial N = 150 Study start date: June 19, 2020	Australia
COVAX-19 vaccine [235]	Vaxine Pty Ltd	Protein Subunit	I Recruiting	Prevention	A randomized, parallel assignment, triple masked trial N = 40 Study start date: June 30, 2020	Australia
V-SARS [236]	Immunitor LLC	Inactivated	I/II Active, not recruiting	Treatment	An interventional, single group assignment for treatment of COVID-19 with pill N = 20 Study start date: May 15, 2020	Canada/ Mongolia
LV-SMENP-DC [237]	Shenzhen Geno-Immune Medical Institute	Lentiviral	I/II Recruiting	Treatment	An interventional, single group assignment for treatment of COVID-19 with novel lentiviral-based DC and T cell vaccines N = 100 Study start date: March 24, 2020	China
BNT162 [238]	BioNTech/ Pfizer	RNA	I/II Ongoing	Treatment	A non-randomized, sequential assignment trial to test the effect of four different BNT162 vaccines against COVID-19 in healthy individuals N = 200 Study start date: April 23, 2020	Germany
aAPC vaccine [239]	Shenzhen Geno-Immune Medical Institute	Lentiviral	I Recruiting	Treatment	An open-label, single-group assignment N = 100 Study start date: February 15, 2020	China

Table 7
Ongoing clinical trials for COVID-19 treatments [240–425]

Treatment goal	Target	Drug	Company	Stage	Reference	Location
Prevention	Pre-exposure prophylaxis	Truvada	Gilead	Phase III	[240]	Spain
Prevention	Nitric oxide	GLS-1200	GeneOne Life Science	Phase II	[241]	USA
Prevention	Broad-spectrum antiseptic	Povidone-Iodine	University of Kentucky	Phase II	[242]	USA
Prevent respiratory infection	Pan antiviral immunotherapy	RTB101	Restorbio	Phase III	[243]	USA
Prevent respiratory illness	Anti-GM-CSF mAb	Otilimab	GSK	Phase II	[244]	USA, Spain
Prevent respiratory illness	Anti-GM-CSF mAb	Mavrilimumab	Kiniksa Pharmaceuticals	Phase II	[245]	USA
Prevent respiratory illness and heart failure	Anti IL-1B mAb	Ilaris	Novartis	Phase II	[246]	USA
Prevent shortness of breath	SSRI	Fluvoxamine	Washington University School of Medicine	Phase II	[247]	USA
Anti-viral growth	EF1A inhibitor	Aplidin	PharmaMar	Phase I	[248]	Spain
Anti-viral growth	IL-29 agonist	Peginterferon Lambda-1a	Eiger BioPharma	Phase II	[249]	USA
Anti-viral growth	Anti-factor XIIa mAb	CSL312	CSL Behring	Phase II	[250]	USA
Anti-viral growth	Plant-derived antiviral	AQCH	Sun Pharma	Phase II	[251]	India
Anti-viral growth	HIV protease inhibitor	Kaletra (Lopinavir – Ritonavir)	Abbvie	Failed trial	[252–255]	Multiple locations
Anti-viral growth	Broad-spectrum antiviral	Arbidol	Pharmstandard	Failed clinical trial	[256]	China, Iran
Anti-viral growth	Broad-spectrum antiviral	EIDD-2801	Ridgeback Bio	Phase I	[257]	United Kingdom
Anti-viral growth	Broad-spectrum antiviral, antiparasitic	Alinia	Romark Laboratories	Phase III	[258–261]	Multiple locations
Anti-viral growth	Broad-spectrum antiparasitic	Ivermectin	Tanta University	Phase II/III	[258]	Multiple locations
Anti-viral growth	Cleaves sialic acid	Fludase (DAS181)	Ansun Biopharma	Phase III	[262, 263]	Multiple locations
Anti-viral growth	Adenosine analog	Remdesivir	Gilead	Approved/ EUA/ Phase III	[264, 265]	Multiple locations
Anti-viral growth	Adenosine analog	Galidesivir	BioCryst Pharmaceuticals	Phase I	[266]	Brazil
Anti-viral growth	Guanosine analog	Virazole	Bausch Health	Phase II	[267]	Canada
Anti-viral growth	Pyrimidine analog	Clevudine	Bukwang Pharmaceutical	Phase II	[268]	Korea
Anti-viral growth	RNA polymerase inhibitor	Avigan (Favipiravir)	Fujifilm	Phase III	[269–272]	Multiple locations
Anti-viral growth	Non-nucleoside reverse transcriptase inhibitor	Elpida (elsulfavirine)	Viriom	Phase II	[273]	Russian Federation
Anti-viral growth	Nucleoside reverse transcriptase inhibitor	Azvodine	Capital Medical University	Phase II	[274]	China
Anti-viral growth	ACE-2 inhibitor	Chloroquine/ Hydroxy-chloroquine	Multiple locations	Failed / Ongoing	[275, 276]	Multiple locations
Anti-viral growth	VEGF inhibitor	Avastin	Roche	Phase II/III	[277, 278]	China, Italy
Anti-viral growth	Inhaled corticosteroid	Alvesco (ciclesonide)	Covis Pharma	Phase III	[279]	Korea, Japan
Anti-viral growth	H2 antagonist	Pepcid (Famotidine)	Northwell Health	Phase II	[280]	USA
Anti-viral growth	Anti-Spike (S), SARS-CoV – 2 mAb	REGN-COV2 (REGN10933 + REGN10987)	Regeneron	Phase III	[281, 282]	USA

Table 7
(Continued)

Treatment goal	Target	Drug	Company	Stage	Reference	Location
Anti-viral growth	Anti-SARS-CoV – 2 mAb	JS016	Junshi Biosciences	Phase I	[283]	China
Anti-viral growth	Anti-SARS-CoV – 2 antibody	LY-CoV555	Eli Lilly, AbCellera	Phase I	[284]	USA
Anti-viral growth	Anti-SARS-CoV – 2 antibody	TY027	Tychan	Phase I	[285]	Singapore
Anti-viral growth	Ion channel blocker	Amiodarone	Nicolaus Copernicus University	Phase II/III	[286]	Poland
Anti-viral growth	Ion channel blocker	Verapamil	Nicolaus Copernicus University	Phase II/III	[286]	Poland
Anti-viral growth	Oral purine nucleotide prodrug	AT-527	Atea Pharmaceuticals	Phase II	[287]	USA
Anti-viral growth	IMPDH inhibitor	Vicromax	ViralClear Pharma	Phase II	[288]	USA
Treat hypoxia	HIF-PH inhibitor	Desidustat	Zydus Cadila	Phase II	[289]	Mexico
Treat hypertension	Renin inhibitor	Aliskiren	Sichuan University	Phase II	[290]	China
Treat pneumonia	Anti-CD6 mAb	Itolizumab	Center of molecular immunology	Phase II	[291]	Cuba
Treat pneumonia	NRP2 modulator	ATYR1923	aTYR Pharma	Phase II	[292]	USA
Treat pneumonia	CRAC channel inhibitor	CM4620	CalciMedica	Phase II	[293]	USA
Treat pneumonia	Bacterial mucosa vaccine	Bactek – R	Immunotek	Phase III	[294]	Dominican Republic
Treat pneumonia	Hep C/HIV protease inhibitors	Ganovo + Ritonavir	Ascleptis	Phase IV	[295]	China
Treat pneumonia	JAK inhibitor	Jakavi	Novartis, Incyte	Phase III	[296]	Multiple locations
Treat pneumonia	Jak1/3 inhibitor	Xeljanz	Pfizer	Phase II	[297]	Italy
Treat pneumonia	Iron chelator	Desferal	Kermanshan University of Medical Sci.	Phase I/II	[298]	Iran
Treat pneumonia	Anti-CD147 antibody	Meplazumab	Tang-Du Hospital	Phase I/II	[299]	China
Treat pneumonia	HIV – 1 protease inhibitor+CYP3A inhitor	Prezcobix	Shanghai Public Health Clinical Center	Phase III	[300]	China
Treat pneumonia	Il-33 inhibitor	MSTT1041A	Genentech	Phase II	[301]	USA
Treat pneumonia	Il-22 receptor agonist	UTTR1147A	Genentech	Phase II	[301]	USA
Anti-inflammatory	Complement (C3) inhibitor	APL-9	Apellis Pharma	Phase I/II	[302]	USA
Anti-inflammatory	Recombinat human C1 inhibitor	Ruconest	Pharming	Phase II	[303]	Switzerland
Anti-inflammatory	Anti-GM-CSF mAb	TJ003234	I-mab Biopharma	Phase I/II	[304]	USA
Anti-inflammatory	DPEP-1 inhibitor	MetaBlok	Arch Biopartnes	Phase II	[305]	Canada
Anti-inflammatory	Tyrosine kinase inhibitor	Masitinib	AB Science	Phase II	[306]	France
Anti-inflammatory	Antioxidant	N-acetylcysteine	MSKCC	Phase II	[307]	USA
Anti-inflammatory	Antioxidant	Viusid and Asbrip	Catalysis SL	Phase II	[308]	Ecuador
Anti-inflammatory	Oral Fenretinide	LAU-7b	Laurent Pharmaceuticals	Phase II	[309]	Canada
Anti-inflammatory	Alpha-1 adrenergic receptor blocker	Prazosin	Johns Hopkins University	Phase II	[310]	USA
Anti-inflammatory	Inhibits DNA synthesis	Etoposide	Boston Medical Center	Phase II	[311]	USA
Anti-inflammatory	Angiotensin II receptor blocker	Telmisartan	Laboratorio Elea	Phase II	[312]	Argentina
Anti-inflammatory	Anti-light (TNFSF 14) mAb	CERC-002	Cerecor	Phase II	[313]	USA
Anti-inflammatory	AntiTNF antibody	Remsima	Celltrion Healthcare	Phase I	[314]	USA
Anti-inflammatory	AT2r Agonist	VP01(C21)	Vicore Pharma	Phase II	[315]	USA

(Continued)

Table 7
(Continued)

Treatment goal	Target	Drug	Company	Stage	Reference	Location
Anti-inflammatory	Live biotherapeutic product	MRx-4DP0004	4D Pharma	Phase II	[316]	United Kingdom
Anti-inflammatory	XPO1 inhibitor	Xpovio	Karyopharm Therapeutics	Phase II	[317]	USA
Anti-inflammatory	Opioid antagonist	Naltrexone	Beaumont Health	Phase II	[318]	USA
Anti-inflammatory	NMDA antagonist	Ketamine	Beaumont Health	Phase II	[318]	USA
Anti-inflammatory	BTK inhibitor	Brukina	BeiGene	Phase II	[319]	USA
Anti-inflammatory	BTK inhibitor	Calquence	Astrazeneca	Phase II	[320, 321]	Multiple locations
Anti-inflammatory	HMGB1 inhibitor	DSTAT	Chimerix	Phase II/III	[322]	USA
Anti-inflammatory	Recombinant humanized GM-CSF	Leukine	Partner therapeutics	Phase IV	[323]	Belgium
Anti-inflammatory	Upregulate RNA splicing	ABX464	Abivax	Phase II/III	[324]	France
Anti-inflammatory	IL-6 inhibitor mAb	Clazakizumab	Vitaeris	Phase II	[325]	USA
Anti-inflammatory	Anti- IL-8 mAb	BMS-986253	Bristol Myers Squibb	Phase II	[326]	USA
Anti-inflammatory	IL-6 inhibitor	Sirukumab	Janssen	Phase II	[327]	USA
Anti-inflammatory	IL-6 inhibitor	Actemra	Roche	Phase III	[328-331]	Multiple locations
Anti-inflammatory	IL-6 inhibitor	CD24Fc	Oncoimmune	Phase III	[332]	USA
Anti-inflammatory	IL-6 inhibitor	Kevzara	Regeneron, Sanofi	Phase II/III	[333]	Multiple locations
Anti-inflammatory	IL-6 inhibitor	Aviptadil	NeuroRX, relief therapeutics	Phase II	[334]	USA
Anti-inflammatory	IL-6 inhibitor	Sylvant	EUSA Pharma	Phase III	[335, 336]	Multiple locations
Anti-inflammatory	IL-6 inhibitor	Levilimab	Biocad	Phase III	[337]	Russian Federation
Anti-inflammatory	IL-6 inhibitor	Olokizumab	R-Pharm	Phase II/III	[338]	Russian Federation
Anti-inflammatory	IL-7 agonist	CYT107	RevImmune	Phase II	[339]	United Kingdom
Anti-inflammatory	TLR 7/8 antagonist	M5049	Merck KGaA	Phase II	[340]	USA
Anti-inflammatory	Anti – GM -CSF	Lenzilumab	Humanigen	Phase III	[341]	USA
Anti-inflammatory	Anti – GM -CSF	Gimsilumab	Roivant, Altasciences	Phase II	[342]	USA
bAnti-inflammatory	Turbulin disruption	Colchicine	Montreal Heart Institute	Phase III	[343]	Canada
Anti-inflammatory	NK1 inhibitor	Tradipitant	Vanda Pharmaceuticals	Phase III	[344]	USA
Anti-inflammatory	C5a mAb	IFX-1	InflaRX	Phase II/III	[345]	Netherlands
Anti-inflammatory	IL-1 inhibitor	Kineret	Sobi	Phase III	[346]	Italy
Anti-inflammatory	IL-1B inhibitor	RPH-104	R-Pharm	Phase II/III	[338]	Russia
Anti-inflammatory	IL-15 superagonist	N-803	ImmunityBio	Phase I	[347]	USA
Anti-inflammatory	IFN γ mAb	Gamifant	Sobi	Phase II/III	[346]	Italy
Anti-inflammatory	CGRP receptor antagonist	Vazegepant	Biohaven Pharma	Phase II/III	[348]	USA
Anti-inflammatory	CCR5 antagonist	Leronlimab (PRO 140)	CytoDyn	Phase II	[349]	USA
Anti-inflammatory	Sphingosine 1-phosphate receptor modulator	Gilenya	Novartis	Phase II	[350]	China
Anti-inflammatory	Tissue regeneration	Mesenchymal Stem cells	Multiple companies	Phase II	[351–365]	Multiple locations
Anti-inflammatory	Mesenchymal Stem cells	RYONCIL	Mesoblast	Phase III	[366]	USA
Anti-inflammatory	A3 adenosine receptor agonist	Piclidenoson	Can-Fite Biopharma	Phase II	[367]	Israel
Anti-inflammatory	Jak2, IRAK-1, CSF1R inhibitors	Pacritinib	CTI Biopharma	Phase III	[368]	USA

Table 7
(Continued)

Treatment goal	Target	Drug	Company	Stage	Reference	Location
Anti-inflammatory	Suprapharmacologic dexamethasone	AVM0703	AVM Biotechnology	Phase I/II	[369]	Denmark
Anti-inflammatory, treat respiratory illness	Corticosteroid	Dexamethasone	University of Oxford	Phase II/III	[370]	Multiple locations
Anti-coagulant	Antithrombotic activity	Enoxaparin	NYU Langone	Phase III	[371]	USA
Block viral entry into cells	Jak1/2 inhibitor	Olumiant	Eli Lilly	Phase III	[372, 373]	Italy, USA
Block viral entry into cells	AXL Kinase inhibitor	Bemcentinib	BerGenBio	Phase II	[374]	United Kingdom
Block viral entry into cells	Serine protease inhibitor	Camostat Mesilate	University of Aarhus	Phase I/II	[375]	Denmark
Block viral entry into cells	Serine protease inhibitor	Nafamostat	University Hospital Padova	Phase II/III	[376]	Italy
Treat respiratory illness	Regenerative medicine	PLX cell therapy	Pluristem Therapeutics	Phase II	[377]	USA
Treat respiratory illness	Nebulized pan-Jak inhibitor	TD-0903	Theravance	Phase I	[378]	United Kingdom
Treat respiratory illness	NMDA antagonist	LEAF-4L6715	LEAF 4Life	Phase I/II	[379]	France
Treat respiratory illness	Humanized IgG4 mAb	Axatilimab	Syndax Pharmaceuticals	Phase II	[380]	USA
Treat respiratory illness	Alkylating agent	Melphalan Inhalation	Fed state Budgetary Institute	Phase II	[381]	Russian Federation
Treat respiratory illness	Complement inhibitor	Soliris	Alexion Pharmaceuticals	Phase II	[382]	France
Treat respiratory illness	Oral selective antitubulin	Veru-111	Veru	Phase II	[383]	USA
Treat respiratory illness	mTOR inhibitor	Sirolimus	University of Cincinnati	Phase II	[384]	USA
Treat respiratory illness	NS	DFV890	Novartis	Phase II	[385]	Denmark
Treat respiratory illness	NS	MAS825	Novartis	Phase II	[386]	USA
Treat respiratory illness	Anti-c5a antibody	BDB-001	Staidson biopharma, Beijing Defengrui Biotech	Phase II/III	[387]	China, Indonesia
Treat respiratory illness	Anti-c5aR antibody	Avdoralimab	Innate Pharma	Phase II	[388]	France
Treat respiratory illness	Interferon beta – 1a	Rebif	Merck KgaA, INSERM	Phase III	[389]	France
Treat respiratory illness	Interferon beta – 1a	SNG001	Synaigen	Phase II	[390]	England
Treat respiratory illness	MARCKS inhibitor	BIO-11006	Biomarck	Phase II	[391]	USA
Treat respiratory illness	C5a inhibitor	Ultomiris	Alexion Pharma	Phase III	[392, 393]	Multiple locations
Treat respiratory illness	PD-1 inhibitor	Keytruda	Merck	Phase II	[394]	Spain
Treat respiratory illness	PD-1 inhibitor	Opdivo	Bristol-Myers Squibb	Phase II	[395]	France
Treat respiratory illness	Anti-angiopoietin 2 mAB	LY3127804	Eli Lilly	Phase II	[396]	USA
Treat respiratory illness	Prostacyclin analog	Ventavis	Hamad Medical Corp	Phase II	[397]	Qatar
Treat pneumonia / sepsis	PD-1 inhibitor	AiRuika	Southeast University	Phase II	[398]	China
Prevention, immunostimulant	TLR agonist	PUL-042	Pulmotect	Phase II	[399]	USA
Anti-viral growth, imunotherapy	NK cell therapy	CYNK-001	Celularity	Phase I/II	[400]	USA

(Continued)

Table 7
(Continued)

Treatment goal	Target	Drug	Company	Stage	Reference	Location
Treat organ failure	Sulfated oxysterol	DUR-928	Durect	Phase II	[401]	USA
Reduce organ failure	AT1R inhibitor	Losartan	University of Minnesota	Phase I	[402]	USA
Reduce organ failure	AT1R inhibitor	Diovan	Radboud University	Phase IV	[403]	Netherlands
Reduce organ failure	SGLT2 inhibitor	Farxiga	Astrazeneca	Phase III	[404]	USA
Anti-viral growth, anti-inflammatory	SK2 selective inhibitor	Yeliva	RedHill	Phase IIa (IND Approval)	[405]	Israel
Anti-viral growth, anti-inflammatory	Recombinant human ACE2	APN01	APEIRON Biologics	Phase II	[406]	Germany, Austria, Denmark
Anti-viral growth, anti-inflammatory	Calpain inhibitor	BLD-2660	Blade therapeutics	Phase II	[407]	USA
Anti-viral growth, anti-inflammatory	DHODH Inhibitor	IMU-83	Immunic	Phase II/III	[408]	Bulgaria, Germany
Anti-viral growth, anti-inflammatory	DHODH Inhibitor	PTC299	PTC Therapeutics	Phase II/III	[409]	USA, Spain
Anti-viral growth, anti-inflammatory	Tyrosine kinase inhibitor	Gleevec	Novartis	Phase III	[410]	USA
Anti-viral growth, anti-inflammatory	Antibodies from recovered patients	Covaescent plasma therapy	Multiple locations	Phase III/ Emergency use	[411–422]	Multiple locations
Anti-viral growth in cancer patients	SUMO inhibitor	TAK-981	Takeda Pharmaceuticals	Phase I	[423]	USA, Canada
Neuroprotective, treat symptoms	Endogenous small molecule	NA-831	NeuroActiva	Phase II/III	[424]	USA
Treat symptoms	Anti-CTGF mAb	Pamrevlumab	FibroGen	Phase II	[425]	USA

Janus kinase JAK 1 and JAK 2 Inhibitor

Baricitinib is an inhibitor of both AP 2 associated Protein Kinase 1 and Cyclin G associated Kinase, helps to prevent endocytosis that is needed for viral assembly. Contraindications for its use are increased creatine kinase levels, an absolute neutrophil count less than 1×10^9 cells/L or an absolute lymphocyte count less than 0.5×10^9 cells/L.⁹ Other considerations are the potential reactivation of tuberculosis, hepatitis B, varicella-zoster, herpes simplex and Epstein Barr virus [154].

Nanomedicine for COVID-19 infection management

It has been suggested that SARS-CoV-2 protein may act like a nanoparticle due to its spherical shape and small size (2–600 nm) and can be taken up by the host cell using a similar mechanism of endocytosis. If a drug could inhibit the endocytosis of SARS-CoV-2 [155], it would open a door for future research as drugs that can act like nano-medications [156] or active therapeutic agents that can be formulated as carriers for delivering, at the target site, using

an effective bio-compatible smart drug nano-carrier [157]. Nanomedicine-based therapy would also minimize the use of excessive COVID-19 drug dosages, which had exhibited adverse effects [155].

Experts have suggested exploring nanomedicine options to manage COVID-19 as a potential therapy using recommended therapeutic agents (synthetic drug, gene, CRISPR-Cas9/gRNA, etc.,) and immuno-acceptable biomaterials to eradicate SARS-COV-2 virus. The tunable drug payload and controlled drug release make nanomedicine suitable for COVID-19 management in a personalized manner [158–162].

Air filtering for COVID-19

The CDC states that COVID-19 is spread predominantly by large respiratory droplets in the proximity of infected individuals (~6 feet). Studies have shown this accounts for >70% spread of the virus. Proper research about the transmission pathways is vital to stop the spread of COVID-19 [163]. A study conducted in an indoor setting has shown that air filtration with particle control technology leads to the reduction of fine (<2.5 microns) and ultrafine particles (<0.25

micron) by 95%. This study has demonstrated the effective elimination of a bacterial bioaerosol surrogate [163].

Proper air filtration methods are necessary to limit the spread of COVID-19. Particle control technology has more significant advantages over high-efficiency particulate air (HEPA) and other means of filtration of the air, as it relies on local electrostatic field manipulation [164].

Treatment for COVID-19 and Alzheimer's disease and dementia

Clinical trials targeting viral pathogenesis are still ongoing, therefore a definitive treatment guideline for COVID-19 is not yet finalized. Concerning morbidity and mortality, the disease has highly impacted the elderly population. Those suffering from mental ailments, especially those in nursing homes, will require a different approach when treating COVID-19. Patients are usually on a cocktail of antipsychotics, antidepressants, and disease-modifying antirheumatic drugs. In patients with Alzheimer's disease (AD), delirium resulting from hypoxia will change management since there is a danger of serious adverse reactions with drug interactions [165]. AD treatment such as donepezil, galantamine, rivastigmine (cholinesterase inhibitors, ChEIs), and memantine, are known for their pharmacokinetic properties in the liver's enzymes cytochrome CYP450 (CYP2C8, CYP2D6, CYP3A4). Cholinesterase inhibitors, antidepressants, and antipsychotics have different levels of interaction with both inducers and/or inhibitors of the enzyme. When adding treatment for COVID-19, the provider must be aware of the risks involved. Antirheumatic chloroquine, and hydroxychloroquine, inhibit CYP2D6, thus requiring adjusting galantamine and donepezil [165]. Although Azithromycin has the least interaction with CYP450, it shares the same cardiac adverse events as the ChEIs, heart-block, bradycardia, QT interval prolongation as well as Torsades de Pointes. Other drugs like lopinavir and ritonavir inhibit CYP3A4 and induce CYP1A2, a combination has the potential of potentiating systemic effects of galantamine and donepezil, adding a ChEI can lead to bradycardia, a less than desirable outcome in patients with a compromised cardiovascular system [165]. Ritonavir requires special consideration since it interacts with several liver enzymes thus requiring a more meticulous adjustment of medications being used in

conjunction. On the other hand, memantine is a preferred drug of choice because of its lower risk of interaction with liver enzymes [165, 166]. Selective serotonin inhibitors like paroxetine and fluoxetine are both inhibitors of CYP2D6 which can both affect glucose levels when used with disease-modifying antirheumatic drugs chloroquine and hydroxychloroquine. Drugs that can safely be used alongside AD treatment include tocilizumab, ribavirin, favipiravir, especially when treating COVID-19 patients in nursing homes [165, 166].

MENTAL HEALTH CONSIDERATIONS

Isolation, working from home, physical distancing, job loss, and critical illness from the virus, could induce long-term psychological effects in many individuals. Social isolation has been linked to a heightened risk of suicide attempts and suicide [167], and several studies address the connection between job loss and a heightened risk of depression [168, 169], anxiety [169], and increased substance abuse [170, 171].

COVID-19 and mental disorders

Long-term isolation and loneliness could act as a trigger for mental disorders such as depression and anxiety in some individuals. A study of 3,005 older adults documented that social disconnection and perceived isolation increased the likelihood of depression and anxiety [172]. A separate study of young adults similarly suggested that social isolation can promote feelings of loneliness and a higher probability of experiencing depression [173].

Viral outbreaks specifically appear to contribute to mental health risks, both directly and indirectly. A study in Canada after the severe acute respiratory syndrome (SARS) outbreak revealed that 28.9% of people exhibited symptoms of post-traumatic stress disorder (PTSD) after being quarantined, and 31.2% exhibiting symptoms of depression [174]. Another study on the aftermath of SARS showed a positive correlation between length of quarantine and symptoms of PTSD, with increased PTSD symptomology in 14.6% of the participants. The psychological symptoms were higher among health-care workers relative to others [175]. After the 2013-2016 Ebola epidemic in Africa, several symptoms of mental distress were reported in Ebola survivors, with symptoms of depression being the most prevalent

at 15–17%. A greater sense of stigmatization and feelings of loneliness were also observed among survivors [176, 177].

Time spent in the ICU is often a traumatic experience, and as such, can more directly increase mental health risks in critically ill COVID-19 patients. A new study on survivors of critical illness admitted to the ICU ($n = 116$) showed that 41.4% of patients reported at least one long term mental health consequence within six months of discharge. Out of the patients experiencing mental health consequences, anxiety, and depression (or the combination of the two) were the most prominent consequences, at 28.4% and 20.7% of patients, respectively. Moreover, the subset of 41 patients receiving mechanical ventilation in this study yielded 22 with long term consequences, a further increase to nearly 54% [178]. In a separate study that included ICU patients receiving mechanical ventilation, signs of anxiety and depression were evident at three months follow up in ~30% and ~21%, respectfully, as well as PTSD in 29.9–34.3% of patients [179]. The scale of negative psychological aftermath due to COVID-19 has yet to be determined; however, some ramifications will undoubtedly arise. A small surveillance study in the UK ($N = 125$) found that 31% of the patients displayed an altered mental status in the form of a psychiatric disorder, including new-onset psychosis (43%), neurocognitive (dementia like) disorder (26%), and an affective disorder (17%) [89].

Health care workers on the front-line with COVID-19 patients will experience an especially large strain, both mentally and physically. Especially in high-risk areas [180], health care workers have displayed symptoms of anxiety [180–182], depression, insomnia [180, 182], and distress from their work environment [181]. Surveillance of psychological conditions following this epidemic as well as measures to minimize psychological distress in the general public may represent an implementable preventive measure now. Especially as experienced by healthcare and other front-line workers.

COVID-19 and domestic abuse

As isolation and lockdown all over the world has been put in place, a perfect storm of stressors for the individual could be a trigger for domestic abuse and violence-related behavior in the home. It could be harder for the abuser to get away from the situation. An increase in domestic violence have currently

been reported on a large scale all over the globe as people are spending more time at home. In Australia, a 75% increase in online searches for domestic abuse has been reported. In Wuhan, China, domestic abuse raised a threefold in February. France and the US reported an increase of between 21% to 36% in domestic violence complaints during the ongoing pandemic [172]. In the UK, calls, emails, and website visits for a domestic violence charity, increased 97%, 185%, and 581%, respectively [183]. In the Czech Republic, there were a doubling of calls to a hot line for abuse victims during the lockdown. In poorer countries like Ukraine and Armenia, a decrease of calls was seen during the lockdown, which could be linked to a lack of internet connection, proximity to the abusive partner, and the referral of the abusers by others, like pharmacy employees or friends [184].

Preventative measures must be put into place, so that people in abusive households have a way to get the help they need. Several countries, including Norway, Germany, France, Italy, and Spain have created a codeword, “MASK 19”, which can be uttered in supermarkets and pharmacies as a signal for help from domestic violence [183]. Another preventative measure could be financial support for people without a job to get out of abusive households, as many people have lost their jobs due to the pandemic and will not be able to support themselves.

COVID-19 and Alzheimer’s disease and dementia.

Age and comorbid medical conditions have consistently been the most impactful factors correlated with poor prognosis, hospitalization, and mortality in COVID-19 patients. Alzheimer’s disease-related dementias (ADRD) elderly patients are an especially vulnerable group because they often have underlying comorbidities [190, 195, 196]. *APOE* $\epsilon 4$, one of the genotypes that puts people at a greater risk of developing ADRD, could possibly be linked to the severity of COVID-19 [185]. Yet more research is called for before concluding that *APOE* $\epsilon 4$ genotype influences disease severity in COVID-19.

Individuals with dementia are also more likely to suffer from strokes, atherosclerosis, diabetes, insomnia, incontinence, fractures, and pneumonia, compared to individuals of the same age without dementia [197], which again puts them at a higher risk for developing severe COVID-19 symptoms if they contract the virus, thus leading to a higher mortality rate in this patient population [190].

People suffering from ADRD are in a specifically vulnerable positions because they heavily rely on others, like family or professional caregivers, for their activities of daily living. This COVID-19 pandemic further exacerbates their vulnerability, due to the synergism of both morbidity and mortality from COVID-19, ADRD and the effects of the pandemic on the social support networks and the healthcare system on which they depend [190]. ADRD was found to be the most common pre-existing condition among patient deaths related to COVID-19 that amounted to 49.5% of all deaths of care home residents in England and Wales, between March 2 and June 12, 2020 [186]. 40% (about 40,000 individuals) of deaths related to COVID-19 in the US have happened in long-term care facilities or nursing homes. It is estimated that more than 2.4 million patients live in long-term care facilities nationwide; this represents a mortality rate of about 450 individuals per day since March to June 2020 [187, 188]. The National Center for Health Statistics (2016) estimates that the percentage of residents of residential care communities with ADRD represents 41.9% and the percentage of nursing home residents with ADRD is 47.8% [189].

The COVID-19 pandemic is affecting services and daily life such as: meals on wheels, either disrupting or delaying it due to increased demand or closure; unavailability of family or professional caregivers due to increased demand, illness, or required isolation; personal savings and investments, with a heightened risk of financial adversity due to the economic slowdowns of the pandemic; increased exposure and risk of infection due to reliance on public transportation services; increased mental health afflictions due to increased isolation and disruption of group activities; the inability to use the technology to stay socially connected and access services, including health care, due to cognitive impairment [190].

Professionals have encountered difficulties while working with adult institutionalized patients, such as isolation induced by the limitation of visits, the shortage of protective equipment and tests, the sustainability of overworking professionals, family members' concern for the residents, complex household situations, and difficulties in accessing care. These challenges are consistent with the social effects of the pandemic. However, the main challenges of individuals with cognitive impairment seems to be understanding and remembering the recommended measures needed to avoid spread and contraction of the virus [190, 194, 198].

Compliance of recommendations from public health authorities to reduce the transmission and spread of COVID-19 may be unachievable for different reasons in ADRD patients. For example, in milder dementias, it might be hard to follow due to apathy or depression. In more severe dementia, the severity of their short-term memory loss and overall cognitive impairment means they are unable to understand, comprehend, or remember most of these recommendations [190].

NUTRITIONAL CONSIDERATIONS

Nutrition intervention, medical nutrition therapy, close management, and timely follow up are all part of the overall approach to treating COVID-19 individuals from the ICU setting to the medicine ward. Appropriate nutritional therapies, especially in the frail elderly, immunocompromised, and individuals with co-morbidities who may already be malnourished or at risk of malnutrition, can ensure survival as well as better and shorter recovery from this illness [191].

Crucial steps for nutrition intervention and management of COVID-19 patients:

1. Screen and check for malnutrition. Patients at risk for worse outcomes and higher mortality following infection with SARS-Cov-2, namely older adults and individuals with co-morbidities must be screened and checked for malnutrition [191]. A registered dietitian (RD) is a trained professional who can identify these individuals by using one of several validated malnutrition screening tools, i.e., Malnutrition Screening Tool or NRS-2002 (Nutrition Risk Screening) [191]. The RD will also perform a nutrition focused physical exam, observing for physical signs of malnutrition, i.e., orbital/temporal wasting, clavicle protrusions, etc. If a patient is determined to be at risk or malnourished, a global nutrition assessment should be conducted to begin interventions on improving patients' nutritional status.
2. In the ICU, vented individuals will need to be provided nutrition support via a nasogastric tube or post-pyloric tube (for prone positioning) [123] within 24–36 hours of admission or 12 hours of intubation. Trophic feeding at 10–20 ml/hour with an isotonic formula, i.e., 1–1.5 kcal/ml with a high nitrogen con-

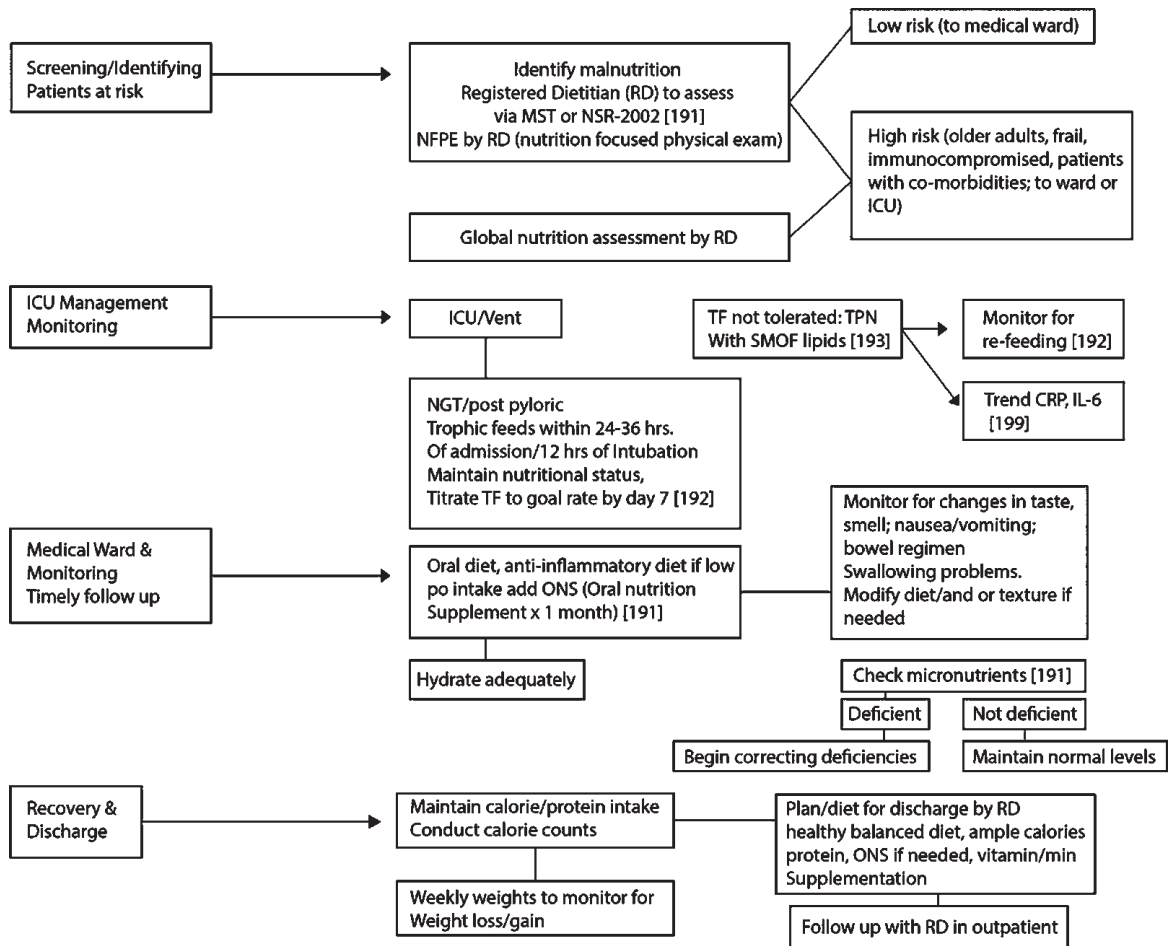


Fig. 6. Nutritional Algorithm.

tent is suggested. During the first week, caloric goals are 15–20 kcal/kg of actual weight, which is about 70–80% of estimated needs. The end of the first week should achieve this goal. By week two, caloric goals are 25–35 kcal/kg or $(REE \times 1.2-2.0)$ and by day 15, 32 kcal/kg or $(REE \times 1.4)$. Protein goals are aimed at 1.2–2.0 gm/kg of actual weight (day 0–4) and 1.5–2.0 gm/kg (>day 4) [192]. For obese patients, the goal is 2.0–2.5 gm/kg of ideal weight. If enteral nutrition is not tolerated, parenteral nutrition is an option. Use Soy/MCT/Olive oil/Fish oil lipids and at least 0.7 gm fat/kg to achieve anti-inflammatory benefits [192, 193]. Refer to Fig. 6 for an overview of the nutritional considerations.

3. Post ICU/medicine ward. Energy needs are 25–35 kcal/kg with protein goals of 1.5–2.0 gm/kg;

obese individuals 2.0–2.5 gm/kg of ideal weight [199]. The oral diet should not be therapeutically restrictive as many patients post ICU do not eat well. Texture modification should be considered for the elderly with chewing/swallowing difficulty. Monitoring patients for loss of taste/smell, nausea, vomiting, diarrhea, and constipation is necessary as all can affect oral intake. Nursing staff to assist with feeding if the patient cannot feed him/herself. Patients should walk within their rooms or the ward if possible, to help improve gut motility. An anti-inflammatory diet would be beneficial with ample servings of fatty fish, fruits, vegetables, beans/legumes, olive oil, nuts, and seeds. Patients that cannot meet caloric/protein goals should be provided with an oral nutrition supplement with 400 calories/30 gm protein

daily for at least one month for repletion [191]. A calorie count can be initiated to verify actual oral intake, and if poor intake is seen, enteral nutrition can be an option to meet caloric/protein goals temporarily. Adequate hydration should be emphasized [191].

4. Check micronutrients and correct deficiencies, if any. In general, low levels of intakes of micronutrients such as vitamin A, E, B6 and B12, zinc, and selenium have been associated with adverse clinical outcomes during viral infections [191]. Some reports show that vitamin C has antimicrobial effects and vitamin D deficiency has been related to several viral diseases. At this time, there are insufficient data for additional supplementation over the standard unless vitamin/mineral deficiency is seen [191, 192].
5. Monitoring COVID-19 patients. Monitor for signs of re-feeding syndrome frequently and replete magnesium, potassium, and phosphorus if depleted in both ICU and post ICU patients if inadequate energy/calorie intake has been suspected for >7 days. Slow feeding rate with enteral nutrition or parenteral nutrition (25% of caloric goals) is necessary [192]. Monitor CRP and IL-6 levels for trends to assess the degree of catabolism and inflammation [199].
6. Weekly/bi-weekly standing scale weights by nursing staff are crucial to monitor for weight loss/gain and to intervene quickly before further weight fluctuation is seen.

The road to recovery for COVID-19 individuals starts with adequate nutrition and correcting their pre-existing malnutrition by providing timely and proper nutrition support, enterally, parenterally, or orally. A solid plan before discharging home by the RD will need to be reviewed with the patient and family, discussing the importance of eating balanced meals with adequate calories, protein, anti-inflammatory foods, and use of oral nutrition supplement and any vitamin and mineral supplementation. Sensitivity to the socioeconomic status of the individual is necessary to identify food insecurity if any. Providing resources to the individual for meal delivery services or obtaining food is beneficial as many may face difficulty purchasing and preparing nutritious meals after the hospital stay. Post-discharge referrals to an outpatient RD should be considered for individuals recovering from COVID-19 who may benefit from ongoing nutritional follow up.

REHABILITATION CONSIDERATIONS

Post-COVID-19 patients present some unique challenges to the rehabilitation team, in addition to multiple typical sequelae of prolonged bedrest and mechanical ventilation.

Patients who have experienced prolonged bedrest and mechanical ventilation typically suffer from profound muscle weakness, balance deficits, orthostatic hypotension, respiratory muscle weakness which mimics a restrictive lung disease, deep vein thrombosis, decubitus ulcer, joint contractures, post-intubation dysphagia, etc.

In addition to the above, patients with COVID-19 in the acute rehabilitation setting have been noted to suffer from a high incidence of dysautonomia (resulting in both orthostatic hypotension and/or severe hypertension and tachycardia), severely reduced activity tolerance, acute stress reaction related to ICU care and intubation (which can be triggered by exertion dyspnea), and diffuse cognitive impairment [200].

Rehabilitation efforts require a multi-disciplinary approach including physical therapy, occupational therapy, speech and language pathologists, and respiratory technicians. Initial efforts are focused on the respiratory muscle strengthening and secretion/dysphagia management [201]. The circulatory system is addressed initially with postural challenges and tends to respond well to this over time. Mobility and functional restoration are achieved with low intensity muscle and aerobic strengthening regimens, which can be intensified over the course of recovery [201].

GENERAL COMPLICATIONS

The most common short-term complications of SARS-CoV-2 infection observed in severe cases included ARDS (100.0% of patients with available ABG data) and respiratory failure (83.3%) [109]. As seen in a study of 21 hospitalized patients in Wuhan, with laboratory-confirmed moderate to severe COVID-19. Less common complications among the severe cases in that study, included secondary infections (27.3%), acute cardiac injury (9.1%) and hypoxic encephalopathy (18.2%), acute kidney injury (18.2%), shock (9.1%) acute liver injury (9.1%) [109], and rhabdomyolysis [202]. Other complications reported:

- Acute hemorrhagic necrotizing encephalopathy is a rare viral complication that has been associated with intracranial cytokine storms, that results in a breakdown of the blood-brain-barrier, without direct viral invasion or demyelination. It presents itself as a hypo attenuated CT image and a T2 FLAIR hyperintense signal, with internal hemorrhage on MRI located most commonly in the thalamus. It can also affect the basal ganglia, brainstem, cerebral white matter, and cerebellum [203]. This case was reported in a female airline worker in her fifties, positive for COVID-19.
- Fulminant myocarditis (FM), is a rare syndrome that presents with cardiac inflammation and displays a mortality rate of approximately 40–70%. FM can be categorized by lymphocytic, eosinophilic, giant cell myocarditis, and sarcoid heart disease. The lymphocytic can be further divided into an infective and noninfective origin. Viral etiology is suspected in most of cases, and biopsy studies of patients with acute myocarditis in Europe indicate that viral etiology ranges between 37.8% and 77.4% Death was associated with cardiac damage induced by a cytokine storm, which is the pathophysiological mechanism in FM. FM was reported in an observational study in 120 patients from Wuhan with severe COVID-19, who exhibited increased IL-6 levels and needed ICU admission. Positive COVID-19 patients with increased Troponin I and new-onset arrhythmias should be followed up closely to prevent cardiac complications [204].
- Spontaneous pneumomediastinum is a self-limiting condition that can cause severe circulatory and respiratory disease. This case was reported in a 38-year-old man from Wuhan, China, who presented exertional angina, palpitations, and respiratory wheezing. On day 11, the patient's chest CT was positive for multiple, bilateral ground-glass opacities with consolidation, and interlobular septal thickening was also observed. Spontaneous pneumomediastinum and subcutaneous emphysema are additionally seen. The exact mechanism of the development of the pneumomediastinum is still unknown [205].
- Acute renal failure, a retrospective laboratory analysis of kidney function, focused on eGFR in 85 COVID-19 patients, showed 23 patients

(27.06%) exhibiting acute renal failure, more frequently in elderly patients (65.22% versus 24.19%, $p < 0.001$), or in patients with comorbidities such as hypertension or coronary heart disease (69.57% versus 11.29%, $p < 0.001$). The damage caused by SARS-CoV-2 infection is due to the induction of severe acute tubular necrosis and lymphocyte infiltration. In their study, Bo Diao and colleagues confirmed the direct infectivity of kidney tubules by SARS-CoV-2, by the viral N-antigens immunohistochemistry. The study also revealed a strong presence of CD68⁺ macrophages in the tubule interstitium as well as deposition of the complement membrane attack complex (MAC, C5b-9) on tubules, which could cause damage [206].

Studies have shown that COVID-19 re-infection is not viable for 7 to 10 days after resolution of the first occurrence. A study in Rhesus monkeys presented no viral replication in all primary tissue samples 5 days after re-infection. This could indicate that a SARS-CoV-2 primary infection could be protective to subsequent occurrences [207].

Cell-mediated and humoral immunity are involved in SARS-CoV-2 infection. To this date, protection from re-infection and a definitive viral clearance timeline has not been clearly established. Based on a study of 11 COVID-19 laboratory-confirmed patients who had experienced two separate symptomatic occurrences, it was hypothesized that either a viral re-infection had occurred or that viral reactivation from tissue reservoirs had taken place [208]. In the case of healthy healthcare workers in settings of prolonged exposure to the virus, mild symptoms can point to a re-infection. In comparison, a re-activation in vulnerable individuals at low risk of infection could have resulted from less than ideal SARS-CoV-2 treatment and management leading to viral replication [208]. Positive RT-PCR test results from recovered patients might have been confounded by cross contamination from another coronavirus, whereas false positive results could have been due to inappropriate sample collection [207].

The long-term complications among COVID-19 survivors are not yet available [48]. The mortality rates for cases globally are 0.1% in patients' ≤ 9 years old to 15% in patients ≥ 80 years old, emphasizing the impact of age on this disease [48, 209].

DISCUSSION AND CONCLUSION

The vast majority of COVID-19 patients undergo different manifestations of disease without a particular order. They may present with ARDS, cytokine storm, acute hypercoagulable state, and autonomic dysfunction, presentations, which must be managed by an array of multidisciplinary teams, including but not limited to infectious disease, pulmonologists, cardiologists, neurologists, nephrologists, gastroenterologists, pain management specialists, psychiatrists, ophthalmologists, internists/hospitalists, orthopedic teams, laboratory medicine and immunologists, as well as dieticians, nursing staff, rehabilitation specialists, and clinical trial teams. Communication, coordination, and collaboration in a timely fashion (C3T), both within care units and when consulting with more experienced teams externally, can enhance patient care and allow prompt treatment evaluation. In lieu of effective treatments, preventive measures, such as physical distancing, facemasks, personal hygiene including thorough washing of hands, and community testing, are highly recommended. Since SARS-CoV-2 may have a substantially higher infectious rate than previously believed both in young children and adults, effective and population-inclusive testing protocols should be put into place to quantify its spread in the population. Otherwise it is difficult to assess actual hospitalization rates without proper data, which is critical, as it will determine how quickly we can return to normality.

COVID-19 has had an enormous impact on physical and mental health, as self-isolation has not only contributed to economic hardship but has possibly also led to higher morbidity and mortality rates from anxiety, suicide, depression, PTSD, and other mental illnesses. The fear of becoming infected may itself discourage those with underlying comorbidities requiring medical attention, such as cardiovascular events, to seek medical care thus potentially aggravating their condition and risking death. Fluid management has shown to have a significant positive impact in the recovery of COVID-19 patients. Conservative fluid management in patients who are prone to pulmonary edema, as well as high risk of developing cardiomyopathy that exacerbates fluid overload, is highly recommended. It must also be noted that pulmonary management in those patients becomes a challenge and extremely difficult to maintain. Dialysis in COVID-19 patients should also be considered

as a therapeutic tool for patients with kidney disease and end-stage renal failure since cytokine-filtering dialysis filters are already available.

The authors suggest that if the patients have loss of consciousness or an altered mental status, then 1) acute hypercapnia, 2) sepsis, and/or 3) seizures, should be suspected and ruled out. Electroencephalography could serve as a tool in assessing the brain function in COVID-19 patients.

It is also important to monitor CRP and IL-6 trends for cytokine storm, and close monitoring of infection symptoms to prevent potential sepsis and subsequent organ failure. Acute hypercoagulable state should be predicted and managed to avoid coagulopathy, stroke, thrombotic events, including limb thrombosis, which could cause compartment syndrome, as well as pulmonary/organ embolism.

Proper pain management in COVID-19 patients is essential. Providers need to be aware of when, and how much pain medications/sedatives to give the patient, since this could have an impact on their physiology and cognition which could potentially mask or cause metabolic encephalopathy.

A comprehensive approach to the management of COVID-19 individuals should involve various treatment modalities. These include a dietary assessment and treatment to effectively reduce complications and improve both short and long-term prognosis essential to ensuring survival, especially in the recovery phase. Furthermore, in order to prevent edema, refeeding syndromes, or micronutrient deficiencies, long-term stay patients in the ICU settings should be routinely monitored for nutritional deficiencies. A review of the literature indicates that common causes of death include cardiovascular, pulmonary, and other organ complications. Therefore, in those COVID-19 patients with underlying comorbidities (e.g., cardiovascular, pulmonary, ADRD, and immunocompromised), it becomes imperative to identify the patients with a high mortality risk. This should be done in order to focus on precise protective measures and management strategies to mitigate negative outcomes in those at risk or those already infected with the virus.

There is an urgent need for a comprehensive, national, and unified guideline for prevention, diagnosis, and treatment of COVID-19. The absence of such guidelines in the US and globally, in addition to the miscommunication and sub-optimal management of the disease by the WHO have created chaos and confusion among healthcare professionals, poli-

cymakers, healthcare institutions, caregivers, and the general public. Unfortunately, the lack of attention to the science and science-based policy in a timely fashion has contributed to the spread of conspiracy theories, misinformation, and mismanagement of the pandemic in the US and abroad.

These have impacted, and will continue to impact, the duration, management, and science-based policy of the pandemic prevention and control. In light of conflicting and inconclusive data and the fact that the main mechanism of viral entry is by the ACE2 receptor, not only do we believe that HCQ may not be effective in the prevention and or treatment of COVID-19, but it could also cause side effects. Hence, we recommend facemasks, physical distancing, and personal hygiene as preventative measures, and other promising medications/therapeutic approaches listed in this paper be used for therapy.

Patients with ADRD need special attention and care during a pandemic to be able to follow the healthcare authorities' recommendations (i.e., CDC, national/local healthcare authorities). Due to poor cognition which result in the incapability of effective physical distancing, hand washing, and correct use of facemasks, they are at a higher risk of contracting COVID-19. Such individuals may not remember their medication, timing of their treatments and follow ups, or understand what is happening around them and to them, which could worsen their overall medical and mental conditions. Therefore, there is a great need for vaccine-based therapy. There is evidence showing the seasonal flu-vaccine and the Pneumococcal vaccine decreases the risk of acquiring AD. More studies are required to establish such connections between COVID-19 and AD as well as other neurodegenerative disorders [210].

Young children, showing little or no symptoms themselves if infected, might also need extra attention and follow up in regards to hand washing and physical distancing to prevent further spread of the virus.

Plenty of resources have been allocated for containment measures, specifically in the development of vaccines. Yet the possibility of not having a functional vaccine, or having one in a timely manner, must also be considered [211]. Therefore, we not only have to pursue vaccine therapy as mentioned in the paper, but also refine our therapeutic protocols including immunotherapy. Such therapies can include the administration of protective antibodies or serum from recovered patients, as well as modulation of beneficial immune responses and blunting of detrimental

immune activity via immunosuppression. In light of newly discovered viral mutations, discussed in this paper, we recommend enhancing B-cell and T-cell response in order to protect and prevent COVID-19 patients from potential re-infection. Novel diagnostics and therapeutics like nanomedicine, discussed in this paper, should be considered for future drugs and diagnostics development of this complex disease.

We believe patients would have a better outcome from well-coordinated, interdisciplinary, specialized and synchronized teams. Communication, coordination, and collaboration in a timely fashion (C3T), could impact the outcome of care for these patients. Through this systematic approach, their underlying conditions could be controlled, disease-related symptoms could be predicted, prevented, detected and treated on time, and before serious complications arise. The authors would like to emphasize the importance of global preparedness for the pandemic of mental health as the result of the COVID-19 so as to respond accordingly and effectively. These include science-based policies, public education on the state of science, and funding scientific research. The use of contactless mass-screening devices, such as thermal imaging cameras, are recommended in indoor public venues. There is a greater need to understand the importance of the transmission pathway of COVID-19 to inform the general population better and make practical guidelines to manage better and limit the spread.

In this paper we have reviewed 28 vaccine clinical trials, several emerging diagnostic tools and therapeutics for COVID-19, which paints a promising picture for the management of this novel disease.

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