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A comprehensive review of pathogenesis and pathophysiology of covid- 19 infection

Manpreet Singh[1], Mangilal[2*], Kanchan[3], Madhu Bala[4], Amit Chawla[5], Rani Payal[6]
[1,3,4]Research scholar, Department of Pharmacy, Maa Saraswati Institute of Pharmaceutical Science, Sitto Road, Abohar, Punjab
[*2]Assistant Professor, Department of Pharmacy,Maa Saraswati Institute of Pharmaceutical Science, Sitto Road, Abohar, Punjab
[5]Professor - Principal, Department of Pharmacy, Maa Saraswati Institute of Pharmaceutical Science, Sitto Road, Abohar, Punjab
[6]Seth GL Bihani SD College of Technical Education, Sriganganagar (Raj.)

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Abstract:

Coronavirus (COVID-19) which is also known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), is the major global health threat. It originated from a city of China named as Wuhan in December 2019 and has been emerging since then worldwide as over more than 190 countries have got affected. COVID-19 has been declared as a Global Health Pandemic by World Health Organization (WHO) on March 11 as till date, 162,553,554 infected patients and 3,371,971 deaths have been recorded worldwide. The symptoms of Coronavirus include fever, cough, myalgia and severe respiratory failure and the diagnosis is confirmed using reverse transcriptase PCR (RT-PCR) test. Till date, no specific treatment is available to deal with this global health pandemic and health system all over the world is trying its best to deal with it and combat it. However, the existing drug therapy provides limited success and is found to be unsatisfactory. In orde0r to eradicate infection, the worldwide focus is on development of vaccine. To prevent the spread of infection, some precautionary and supportive measures such as social distancing, self-quarantine, avoid crowded places, avoid travelling unnecessarily are being practiced and exercised, besides, probationary drug therapy. At the initial stages due to state of emergency many patients have been treated with antiviral drugs, antibacterial drugs and corticoids such as lopinavir, ritonavir , chloroquine(CQ), hydroxychloroquine (HCQ), remdesivir, favipiravir, ribavirin, interferons(IFN's), corticosteroids, oseltamivir etc. This study outlines the types of COVID-19 vaccines, strengths and shortcomings of every COVID-19 vaccine development platformand analyses the challenges ahead.

Keywords:

Virus, hypertension, covid-19, infectivity, metalloproteinase.

1. Pathogenesis of COVID-19 infection:

SARS-CoV-2 infections reaches host cells via the S spike protein, where it is assisted in internalisation by the TMPRSS2 protease. The virus's high infectivity is due to mutations in the receptor binding domain and the S spike protein acquiring a furan cleavage site. In predisposed patients, the virus-ACE2 interaction can reduce ACE2's anti-inflammatory role and increase angiotensin II's effects (Li Wenhui et al.,2003). With the difficulty we face with COVID-19, others have advocated for the use (or discontinuation) of Angiotensin II receptor type 1 (AT1 receptor) blockers and ACE inhibitors in patients with hypertension receiving COVID-19.

Currently, the European Society of Cardiology's Council on Hypertension recommends that patients continue their antihypertensive care unchanged, since there is no evidence to support its cessation.

However, additional study is needed to substantiate these recommendations.Chemoattractant protein 1, macrophage inflammatory protein 1, and increased expression of programmed cell death 1, T-cell immunoglobulin, and mucin domain 3 (Tim-3) were identified (Chiappelli F et al., 2020). These changes contribute to the pathogenesis of lung injury, myocyte injury caused by hypoxia, the body's immune response, increased myocardial cell damage, and intestinal and cardiopulmonary changes.

SARS-CoV-2 is mainly a lung, vasculature, and immune system virus (Wang X et al., 2020). The initial step in viral replication is viral protein spike (S) binding to the surface of respiratory cells (Fantini J et al., 2020). It was previously hypothesised that SARS-CoV-2 may use angiotensin-converting enzyme 2 (ACE2, EC 3.4.17.23) found in a variety of mammals, except mice and a few birds, such as pigeons (Qiu Y et al., 2020). SARS-CoV-2 has a 10–20- fold higher affinity for ACE2 than SARS-CoV (South AM et al., 2020).

ACE2 is a metalloproteinase with approximately 60% homology to the angiotensin- converting enzyme carboxy-peptidase (ACE, EC 3.4.15.1). ACE2 is a type I transmembrane glycol-protein with a single extracellular catalytic domain. It contains 805 amino acids (Sun P et al.,2020). It has been documented to be expressed in the lungs, cardiovascular system, gut, kidneys, central nervous system, and adipose tissue (South AM et al.,2020). It is the central active peptide of the renin–angiotensin system (RAS) or the renin–angiotensin–aldosterone system (RAAS) (South AM et al.,2020). Angiotensin II (Ang II) is the primary effector of the RAAS, promoting hypertension in part by decreasing baro-receptor sensitivity necessary for heart rate maintenance and increasing vasoconstriction, sodium retention, oxidative stress, inflammation, and fibrosis. Numerous studies indicate that ACE2 plays a critical role in efficiently degrading Ang II to Ang- (1-7), which neutralises Ang II's impact (*Fig.1*) (South AM et al.,2020). Ang-(1–7) acts on the Mas-receptor, lowering blood pressure slightly via vasodilation, promoting sodium and water excretion by the kidney, and also attenuating inflammation via nitric oxide output (*Fig.1*) (South AM et al., 2020). (*Fig.1*) (South AM et al., 2020).

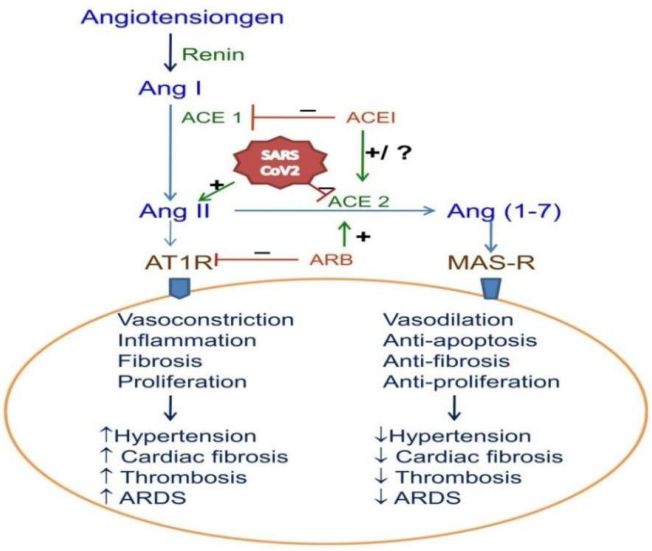

Figure. 1: Functional scheme of the renin-angiotensin system. The protease renin converts the precursor angiotensinogen to Angiotensin I (Ang I) and subsequently converted to Ang II by dipeptidyl carboxypeptidase angiotensin converting enzyme (ACE). Ang II binds to the AT1 receptor (AT1R) to stimulate inflammation, fibrosis, oxidative stress and an increase in blood pressure. Ang II are converted to Ang-(1-7) via endopeptidases (NEP) and the moncarboxypeptidase ACE2, respectively. Ang-(1-7) binds to the Mas-R to exert anti- inflammatory and anti-fibrotic actions, stimulate the release of nitric oxide and reduce blood pressure. SARS-CoV-2 binds to ACE2 to stimulate internalization of both the virus and peptidase causing deleterious effects. Angiotensin converting enzyme inhibitors (ACEIs)/Angiotensin receptor blockers (ARBs) regulate the metabolic pathway

The SARS-S1 CoV's domain binds to the host cell's ACE2 receptor (Hoffmann M et al.2020). The binding of the SARS-CoV-2 spike protein to ACE2, followed by a conformational change in the S-glycoprotein that allows ACE2 to be proteolyzed by transmembrane serine protease 2 (TMPRSS2) to generate the S1 and S2 subunits, is a critical step in S2-induced membrane fusion and virus internalisation through endocytosis in the pulmonary epithelium. The virus's entrance into cells stimulates virus replication and cell-to-cell transmission further (Hoffmann M et al.2020), and is thought to suppress ACE2 expression. This inhibition of ACE2 results in a decrease in tissue level and a decrease in Ang- (1–7) development, as well as an increase in Ang II levels. Further conversion of Ang-(1–7) by ACE results in the formation of less biologically active peptides. This process has the potential to initiate an Ang II–AT1R-mediated inflammatory response in the lungs and to stimulate parenchymal injury in the future (South AM et al.,2020). The pathogenesis is complex and includes two interconnected processes: lung inflammation and immune deficiency, both of which are associated with an abnormal immune response and excessive development of pro-inflammatory cytokines(Wang X et al.,2020), as well as an altered redox balance in infected cells due to NAD? Deficiency. Biosynthesis, poly (ADP-ribose) polymerase (PARP) action, and proteasome and mitochondrial dysfunction all contribute to the escalation of inflammation and lipid peroxidation, resulting in cell harm (Nasi A et al.,2020). (Ji HL et al.,2020) lymphopenia in these patients (Xiong Y et al.,2020). SARS-CoV-2 exhibits neurotropic properties and has the potential to induce neurological diseases. CoV are often detected in the brain or

cerebrospinal fluid, according to reports (Wu Y et al.,2020). Another characteristic of extreme COVID-19 is coagulopathy, as measured by elevated Plasmin (ogen) levels in these patients (Ji HL et al.,2020).

2. Age, gender and comborbidities are all associated with pathogenesis:

SARS-CoV-2 has been linked to poor outcomes and a higher mortality risk in older adults (over 60 years of age) and those with comorbid conditions such as hypertension,

cardiovascular disease, diabetes mellitus, chronic respiratory disease, or chronic kidney disease (Ji HL et al.,2020) (Shahid Z et al.2020). The COVID-19 virus tends to infect children in a mild manner. Adult patients are thought to have a suppressed adaptive immune system and an impaired innate immune response (Dhochak Net al.,2020). Women are thought to be less susceptible to infectious diseases than men due to their dissimilar innate immunity, steroid hormones, and factors associated with sex chromosomes. In females, the immune regulatory genes encoded by the X chromosome result in a lower viral load and less inflammation than in men, whereas CD4? T cells are increased, resulting in a stronger immune response. In contrast to men, women have a higher TLR7 expression level and its biallelic expression is associated with improved immune responses and enhanced resistance to viral infections (Conti P et al.,2020) (Babapoor- Farrokhran S et al.,2020).

COVID-19 can exacerbate complications in individuals with diabetes by disrupting the ACE2 activation pathway, resulting in an inflammatory response and pancreatic b-cell dysfunction, which may exacerbate COVID-19-related complications such as vasculopathy, coagulopathy, and psychological stress (Cuschieri S et al.,2020). Chronic low-grade inflammation associated with diabetes and obesity can also contribute to an exacerbated 'cytokine storm' in COVID-19 patients (Das L et al.,2020).

Smokers' and COPD patients' respiratory epithelium cells display a higher level of the ACE2 receptor. Nicotine binds to and improves the activity of nicotinic acetylcholine receptors (nAChR), specifically the a7 subtype (a7-nAChR), found in the lungs and various other tissues, most notably the central nervous system. Increased ACE2 receptor expression is mediated by stimulation of the a7-nAChR, which enables the entry of SARS-CoV-2 into the respiratory epithelium (Hasanagic S et al.,2020). ACE2 expression on endothelial cells is associated with viral endothelitis and may precipitate vascular dysfunction, which manifests as acute respiratory distress syndrome (ARDS) (Das L).

A meta-analysis of 1558 patients with COVID-19 from six studies found no evidence of an association between an elevated risk of COVID-19 and liver disease, malignancy, or renal disease (Wang B et al.,2020).

Clinical signs of COVID-19 infection include fever, non-productive cough, dyspnea, myalgia, and fatigue, as well as usual or reduced leukocyte counts and radiographic proof of pneumonia (C. Huang et al.,2020), which are close to those of SARS-CoV and MERS-CoV infections (J.S. Peiris et al.2004).

Thus, although the pathogenesis of COVID-19 is unknown, the similarities between SARS-CoV and MERS-CoV will provide us with valuable information about the pathogenesis of SARS-CoV-2 infection, thereby facilitating our identification of COVID-19.

3. Coronavirus infection and replication:

Coronavirus S protein has been shown to be a critical factor in virus entry into host cells (E. de Wit et al., 2016). The envelope spike glycoprotein binds to its cellular receptor, ACE2 in the case of SARS-CoV (W. Li et al.,2003) and SARS-CoV-2 (F. Wu et al.,2020), CD209L in the case of SARS-CoV (S.A. Jeffers et al.,2004), and DPP4 in the case of MERS-CoV(V.S. Raj et al.,2013). Initially, it was determined that SARS-CoV entered cells through direct membrane fusion between the virus and the plasma membrane (G. Simmons et al.,2004). Belouzard et al. (S. Belouzard et al.,2009) discovered that a crucial proteolytic cleavage event at position (S20) of the SARS-CoV S protein mediated membrane fusion and viral infectivity. Additionally, MERS-CoV has developed an irregular two-step furin activation process for membrane fusion (J.K. Millet et al.,2014). Apart from membrane fusion, SARS-CoV entry was facilitated by both clathrin-dependent and -independent endocytosis (H.Wang et al.,2008) (K. Kuba et al.,2010). After the virus infects cells, the RNA genome is released into the cytoplasm and converted into two polypeptides and structural proteins, at which point the viral genome starts to replicate (S. Perlman et al.,2009). The newly developed envelope glycoproteins are incorporated into the endoplasmic reticulum or Golgi membranes, and the nucleocapsid is formed by combining genomic RNA and the nucleocapsid protein. Afterwards, viral particles germinate in the endoplasmic reticulum-Golgi compartment

(ERGIC). Finally, the vesicles containing the virus particles fuse with the plasma membrane, allowing the virus to be released (E. de Wit et al.,2016).

4. Presentation of antigens during coronavirus infection:

When the virus is within the cells, it can present its antigen to the antigen presentation cells (APC), which are a critical component of the body's anti-viral immunity. Major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) presents antigenic peptides that are then recognised by virus-specific cytotoxic T lymphocytes (CTLs). Thus, understanding the antigen presentation of SARS-CoV-2 will aid in our understanding of the pathogenesis of COVID-19. Regrettably, there is no study on it, and we can only gather knowledge from previous studies on SARS-CoV and MERS-CoV. SARS-CoV antigen presentation is primarily dependent on MHC I molecules (J. Liu et al.,2010), but MHC II also plays a role. Numerous HLA polymorphisms, including HLA-B*4601, HLA-B*0703, HLA- DR B1*1202 (N. Keicho et al.,2009), and HLA-Cw*0801 (Y.M. Chen et al.,2006), have been linked to SARS-CoV susceptibility, while the HLA-DR0301, HLA-Cw1502, and HLA- A*0201 alleles are

associated with immunity from SARS infection (S.F Wang et al.,2011). MHC II molecules, such as HLA-DRB1*11:01 and HLA-DQB1*02:0, are associated with MERS-CoV infection susceptibility [52A.H. Hajeer et al.,2016]. On the other hand, MBL (mannose-binding lectin) gene polymorphisms associated with antigen presentation are associated with an increased risk of SARS-CoV infection (X. Tu et al.,2015). These studies will contribute significantly to our understanding of the prevention, treatment, and mechanism of COVID-19.

5. Humoral and cellular immunity:

Antigen presentation activates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. Similar to other acute viral infections, the SARS-CoV virus antibody profile exhibits a typical pattern of IgM and IgG development. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can persist for a long period of time, indicating that the IgG antibody can primarily serve as a protective factor (G. Liet al.,2003), and that the SARS-specific IgG antibodies are predominantly S- and N-specific (E. de Wit et al.,2016). In comparison to humoral responses, there are more studies on coronavirus cellular immunity. The most recent study indicates that the amount of CD4 and CD8 T cells in the peripheral blood of SARS-CoV-2-infected patients has decreased substantially, despite the fact that their activation status is excessive, as indicated by high proportions of HLA-DR (CD4 3.47 percent) and CD38 (CD8 39.4 percent) double-positive fractions (Z. Xu et al.,2020). Similarly, in patients infected with SARS-CoV, the acute phase response is associated with a significant decrease in CD4 and CD8 T cells.

6. Cytokine storm in covid-19:

According to the Lancet study, ARDS is the primary cause of death in COVID-19. Six of the 41 SARS-CoV-2-infected patients admitted during the outbreak's early stages died of ARDS (C. Huang et al.,2020). ARDS is the most frequently encountered immunopathological manifestation of SARS-CoV-2, SARS-CoV, and MERS-CoV infections (Z. Xu et al.,2020). One of the primary mechanisms underlying ARDS is the cytokine storm, a lethal uncontrolled systemic inflammatory response induced by the release of large amounts of pro-inflammatory cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a, TGFb, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9,CXCL10, etc.) (C.Huang et al.,2020)(A.E. Williams et

al.,2014)(R. Channappanavar et al.,2017)(M.J. Cameron et al.2008). Similar to those infected with SARS-CoV, those with extreme MERS-CoV infection have significantly higher serum levels of IL-6, IFN-a, CCL5, CXCL8, and CXCL-10 than those with mild-moderate disease (C.K. Min et al.,2016). The cytokine storm will trigger the immune system's violent assault on the body, resulting in ARDS and multiple organ failure, and ultimately death in extreme cases of SARS-CoV-2 infection, just as it does

with SARS-CoV and MERS-CoV infection (Z. Xu et al.,2020).

7. Immune evasion by coronavirus:

IFN-I (IFN-a and IFN-b) protects against SARS-CoV and MERS-CoV infection, but inhibits the IFN-I pathway in infected mice (R. Channappanavar et al.,2016)(R. Channappanavar et al.,2019). MERS-CoV accessory protein 4a can inhibit IFN induction at the level of MDA5 activation through direct interaction with double-stranded RNA (D. Niemeyer et al.,2019). Additionally, ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit IFN regulatory factor 3 (IRF3) nuclear transports and promoter IFN b's activation (Y. Yang et al.,2013). Coronaviruses may also have an impact on how antigens are presented. For example, following MERS-CoV infection, gene expression associated with antigen presentation is down- regulated (V.D. Menachery et al.,2018). As a result, eradicating SARS-immune CoV-2's evasion is critical for its treatment and production of unique drugs.

8. Pathophysiology of covid-19 infection:

- **Transmission of infection:**

Infection is primarily transmitted person to person through respiratory droplets. The faecal-oral route is also an option. The virus has been detected in sputum, pharyngeal swabs, and faeces (D'Amico F et al.,2020). Vertical transmission of SARS- CoV-2 has been identified (Li M et al.,2020) and verified by the presence of COVID-19 on a nasopharyngeal swab. COVID-19 has a median incubation time of 5.2 days; the majority of patients experience symptoms between 11.5 and 15.5 days. As a result, it has been recommended that those exposed to infection be quarantined for 14 days.

As 2019-nCoV enters the human body, it interacts with ACE2 receptors and releases its RNA into epithelial cells (ECs), where it replicates and spreads to adjacent cells, spreading from

the nasal passage to the alveolar region of the lung (Mason RJ,2020). Alveoli mediate gaseous exchange, but infection with 2019-nCoV results in a vascular integrity defect (increased permeability and leakage), which results in pulmonary oedema, activation of disseminated intravascular coagulation (DIC), pulmonary ischaemia, hypoxic respiratory failure, and progressive lung harm (Teuwen LA et al.,2020). Additionally, it reaches the bloodstream through infected ECs and spreads throughout the body, including the brain, gastrointestinal tract, heart, kidney, and liver, causing cerebral haemorrhage, neural disorder, ischemic stroke, coma, paralysis, and ultimately death (Zaim Set al.,2020). Additionally, the vulnerability and incidence of 2019- nCoV infection in individuals are strongly influenced by co-morbidities such as hypertension, diabetes, and lung diseases, as well as by age and dysregulation of the innate immune response. This may be because the ACE2 receptor (an integral membrane protein) is overexpressed on the surface of many organs, including the lung, heart, kidney, and intestine, as well as host ECs (Varga Z et al.,2020). By binding to ACE-2, the 2019-nCoV infects ECs and causes localised inflammation, endothelial activation, tissue damage, and disordered cytokine release. The extreme

aggravation of the "cytokine storm" through secretion of vascular endothelial growth factor (VEGF), monocyte chemoattractant protein–1 (MCP-1), and IL-8, as well as decreased E-cadherin expression on ECs, contribute to increased vascular permeability and leakage, which contribute to the pathophysiology of hypotension and pulmonary dysfunction in acute respiratory distress syndrome (ARDS). The majority of COVID19 patients die as a result of ARDS, which pulmonary ECs contribute to by altering vessel barrier integrity, promoting coagulation, inducing vascular inflammation, and reconciling inflammatory cell infiltration (Leisman DE et al.,2020). Thus, it is important to consider the multiple complications associated with 2019-nCoV infection of the vasculature. When compared to ECs from other organs, lung ECs exhibit greater immunomodulatory signatures, including increased expression of genes involved in major histocompatibility complex (MHC) class II-mediated antigen processing, loading, and presentation. This indicates that a subset of lung ECs functions as semi- professional antigen-presenting cells in the presence of respiratory pathogens. Additionally, it has been proposed that ECs play a critical role in the pathogenesis of acute respiratory distress syndrome (ARDS) and multi-organ failure in patients with COVID-19. In extreme COVID-19 infection, coagulation pathways are activated, potentially leading to the production of DIC. As a result of DIC and inflammatory cell clogging/congestion of small capillaries, as well as possible thrombosis in larger vessels, lung tissue ischaemia occurs, triggering angiogenesis and possible EC hyperplasia (Ackermann M et al.,2020)(Jose RJ et al.,2020). Numerous mechanisms for increased vascular permeability and leakage have been suggested in extreme COVID-19 patients, as Teuwen et al. explain in detail (2020). 61 In brief, the 2019- nCoV will directly affect ECs, causing EC dysfunction, lysis, and death; ii) Additionally, in order to reach the host cells, the 2019- nCoV binds to the ACE2 receptor, inhibiting its activity and thus activating the kallikrein–bradykinin pathway, resulting in increased vascular permeability. iii) activated neutrophils recruited to pulmonary endothelial cells (ECs) generate histotoxic mediators such as reactive oxygen species iv) immune cells, inflammatory cytokines, and vasoactive molecules

increase the contractility of ECs and the loosening/gap of inter-endothelial junctions; v) the cytokines IL-1 and TNF activate glucuronidases that degrade the glycocalyx but also unregulated hyaluronic acid synthase 2, resulting in increased hyaluronic acid deposition in the extracellular matrix (Pober JS et al.,2007) (Teuwen LA et al.,2020). Additionally, elevated cytokine levels accelerate the destructive process, resulting in additional EC dysfunction, DIC, inflammation, and vasodilation of the pulmonary capillary bed. When these conditions are combined, they eventually result in multi-organ failure and death as a result of alveolar dysfunction and ARDS with hypoxic respiratory failure. Additionally, it has been suggested that denudation of the pulmonary vasculature can activate the complement system, promoting the accumulation of neutrophils and pro-inflammatory monocytes that contribute to the cytokine storm, as was observed during influenza virus infection, where pulmonary ECs induce an amplification loop involving interferon- producing cells and virus-infected pulmo (Mehta P et al.,2020). Normalization of the vascular wall by metabolic interventions can be considered an additional route of action, paving the way for potential therapeutic opportunities in addition to anti- inflammatory, anti-

cytokine, and ACE inhibitors, among others (Pober JS et al.,2007). Additionally, some indirect evidence indicates a link between ECs, pericytes, and COVID-19. As a result, the effects of 2019-nCoV on the entire vasculature need additional attention (Mason RJ,2020).

9. Conclusion:

COVID-19 is a contagious respiratory illness caused by the SARS-CoV-2 virus, characterized by symptoms that can include fever, cough, fatigue, breathing difficulties, and a loss of taste or smell. The disease spread globally, leading to the COVID-19 pandemic. People can get infected again if the virus mutates, and some pets can also be infected. COVID-19 treatments include oral antivirals like Paxlovid and Molnupiravir for high-risk individuals, intravenous antivirals like remdesivir for those in healthcare facilities, and other medications such as baricitinib, tocilizumab, and corticosteroids for severe cases. Treatment options depend on the severity of the illness and a person's risk factors for developing severe COVID-19.

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