



Coronavirus Disease 2019 (COVID-19): Pathogenesis, Immune Responses, and Treatment Options

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Authors' contributions

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ABSTRACT

Background: The emergence and the spread of the novel coronavirus or the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a devastating impact on the economy and has become a pressing issue globally. Due to the significant increase in the number of confirmed cases and death tolls worldwide, and certain countries reporting second waves, there is an immediate need for an effective vaccine or other therapeutic intervention to control the spread of the disease. Improving our understanding on the host's anti-viral immune response on SARS-CoV-2 infection, the potential immune evasion mechanisms adopted by the virus, and the speculated role of antibody dependent enhancement (ADE) in coronavirus disease 2019 (COVID-19) pathogenesis will aid in identifying and designing effective therapeutics.

Aim: This review aims to provide an in-depth view of the current knowledge available on the range of host defense mechanisms activated by SARS-CoV-2 infection and various immune evasion

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mechanisms utilized by the virus. In addition, it also highlights the postulated role of ADE in viral pathogenesis and covers the different preventive and therapeutic options available for the treatment of COVID-19 based on current literature.

Discussion: The ongoing COVID-19 pandemic serves as a timely reminder on the constant evolutionary process the virus undergoes to emerge as a novel strain and to spread undetected within the population. Similar to other infectious diseases, the host defence mechanism is triggered, and it plays a central role in dampening viral replication by recruiting immune cells and activating anti-viral mechanisms to control the spread of infection by SARS-CoV-2. However, the virus has adopted different immune evasion mechanisms to circumvent host surveillance to successfully establish infection. Hence, understanding the host's immune responses triggered by SARS-CoV-2 infection is critical for identifying and designing novel and effective therapeutics. Currently, over 70% of the population are either asymptomatic or they showcase mild to moderate symptoms and reasons for why some people can mount immune responses more quickly than others are unknown. However, a growing body of research speculates that the ADE mechanism may facilitate the SARS-CoV-2 entry and can contribute to severe clinical manifestations. With the constant rise in the number of confirmed cases, there is an immediate need for an effective vaccine to mitigate the spread of the virus. Presently, there is no treatment for COVID-19 although several vaccine candidates are in clinical trials. Therefore, preventive measures like social distancing, isolation, and travel restrictions, may be the key to controlling the rapid spread of COVID-19.

Keywords: *Antibody-dependent enhancement; Coronavirus; COVID-19; SARS-CoV-2; treatment; type 1 interferon.*

1. INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a member of the *Coronaviridae* family. The initial cases that appeared in December 2019 were traced to a seafood market in Wuhan, Hubei Province, China. Since then, the number of cases has been on a steady rise daily with some countries reporting second waves of the infection. As of July 30, 2020, over 10.1 million cases and 503,967 deaths were reported across 188 countries [1] (Fig. 1). While there have been epidemics caused by coronaviruses (CoVs) in the past like the severe acute respiratory syndrome (SARS) in 2002 and the Middle East respiratory syndrome (MERS) in 2012, SARS-CoV-2 is by far the most infectious human coronavirus (HCoV) known.

The host immune system plays an essential role in limiting SARS-CoV-2 replication by activating the anti-viral strategy and recruiting the immune cells. However, SARS-CoV-2 has adopted different immune evasion mechanisms to circumvent host surveillance, proliferate, and elicit inflammatory responses, particularly in the lungs resulting in pneumonia. Currently, more than 70% of the population are either asymptomatic or they showcase mild to moderate symptoms, as opposed to some individuals who experience hyper-inflammation

induced by a cytokine storm [2]. Understanding the correlation between differential inflammatory gene expressions among patients and severity of the disease is crucial for the development of potential therapeutic interventions. Reasons for the variation in the host immune response is yet to be elucidated, but there is mounting evidence that outlines the speculated role of antibody-dependent enhancement (ADE) in disease pathogenesis. Owing to the alarming rise in the number of confirmed cases and death tolls globally, and also reports of second waves in certain countries, there is an immediate need for an effective vaccine or other therapeutic interventions. Currently, there is no approved vaccine for the treatment of COVID-19, although several vaccine candidates are currently under clinical trials to test their immunogenicity, efficacy, and safety profile prior to being licensed and approved for global distribution. Some of the potential vaccine candidates currently under clinical investigation include Ad5-nCoV from CanSino Biologicals (NCT04341389; Phase II), mRNA-1273 from Moderna (NCT04470427; Phase III), ChAdOx1-S from the University of Oxford/AstraZeneca (2020-001228-32; Phase II/III), INO-4800 from Inovio (NCT04447781; Phase I/II), and NVX-CoV2373 from Novavax(NCT04368988; Phase I/II). Hence, improving our understanding on the host's anti-viral immune response against SARS-CoV-2, the potential immune evasion mechanisms, and the various treatment options is necessary as they

will aid in designing effective therapeutics for treating COVID-19.

In this review, we briefly summarize our knowledge of host immunological responses triggered upon infection by SARS-CoV-2. We also discuss the pathogenesis and highlight the speculated role of ADE in the COVID-19 pathogenesis. We also provide a comprehensive overview of the various preventive and therapeutic modalities for the disease treatment.

2. PATHOGENESIS OF COVID-19

The first HCoV identified in the early 1960's were HCoV-229E and HCoV-OC43. They are a part of four well-characterized seasonal HCoVs (sHCoV), including HKU1-CoV and NL63-CoV, each of which is frequently associated with the common cold and are held susceptible for 2-18% of the respiratory tract infections[3]. While the pathogenic potential of these strains is moderately low, they can cause complications such as sepsis or severe respiratory distress in the elderly, infants, immunocompromised individuals, or in people with a pre-existing pulmonary condition. Although the estimate of their contribution to respiratory illnesses varies, sHCoVs widely remain asymptomatic in more than half of cases[4]. This is in sharp contrast to the clinical manifestations exhibited by MERS-CoV, SARS-CoV, and SARS-CoV-2, which

report higher mortality and case-fatality ratios compared to sHCoVs.

Understanding mechanisms underlying COVID-19 pathogenesis can provide insights in explaining the high levels of ferritin, D-dimer, pro-inflammatory cytokines, low levels of natural killer (NK) cells, and cytotoxic T cells. The increase in the levels of these indicate the presence of Macrophage Activation Syndrome (MAS) and cytokine storm [5]. The most immunogenic part of SARS-CoV-2 is spike protein (S), which binds to Angiotensin Converting Enzyme-2 (ACE2). Proteolytic cleavage of S proteins by proteases like transmembrane protease serine 2 (TMPRSS2), furin, or cathepsins is required for their activation. TMPRSS2 is a recently identified trypsin-like protease that has been shown to be important for the functional activation of SARS-CoV-2[6], which aids the entry of the virus into the host cell. ACE-2 receptor expression is distributed across the surface of cardiac, renal, alveolar epithelial type II cells[7]. Like the other coronaviruses, the SARS-CoV-2 central mode of transmission occurs through respiratory droplets[8]. A study found ACE2 receptor expression was upregulated in the epithelial cells in the salivary gland ducts, indicating saliva to be the transient medium for virus transmission[9]. Indirect transmission happens when a person is in contact with a surface that is contaminated with the virus.

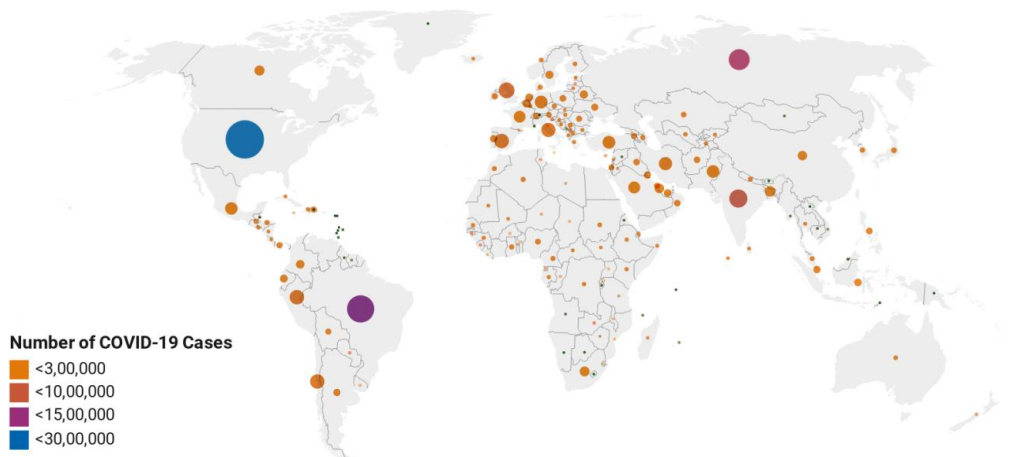


Fig. 1. A global distribution of COVID-19 severity country-wise based on the number of reported confirmed cases. There is a significant rise in the count of confirmed cases in the USA, thereby marking it the world's most affected country till date. Data source: World Health Organization (WHO) Coronavirus dashboard [1]

The viral replication is presumed to originate from the upper respiratory tract, and upon the disease progression, it multiplies in the lower respiratory tract. After infection, the average incubation period is approximately 4-5 days before the symptom onset[10,11,12] with 97.5% symptomatic individuals showcasing the clinical features within 11.5 days. During the time of hospital administration, COVID-19 patients exhibit fever, dry cough, and to some extent, difficulty in breathing, dizziness, and headache[5,13,14]. Post 5-6 days of symptom onset, SARS-CoV-2 reaches a peak viral load significantly earlier than SARS-CoV which reaches its peak after 11 days of symptom onset[15–17]. Severe/critically ill COVID-19 patients progress to acute respiratory distress syndrome (ARDS), approximately 8-9 days post symptom onset[18]. After binding of spike glycoprotein to the ACE2 receptor, the virus enters into the cytoplasm of the cell. Following this, the viral ribonucleic acid (RNA) genome is released and replicated, resulting in the formation of new viral particles. The cell undergoes disintegration and the virus is spread to other cells. As the immune system recognizes the viral particles, innate and adaptive mediated immune responses are triggered resulting in the release of a huge number of chemokines and pro-inflammatory cytokines. In some cases, the heightened activation leads to cytokine storm develops resulting in multi-organ failure and death[19,20].

The pathophysiology of SARS-CoV-2 infection is similar to SARS-CoV, with heightened immune response resulting in damage to the airways[21]. Hence, the disease severity not only depends upon the viral load but also on the host immune response. Although several groups of populations are susceptible to COVID-19, efforts to contain transmission are primarily aimed at vulnerable groups such as the elderly, health care providers, children, and pregnant women. A study conducted in late January obtained data on the clinical features and outcome for 1,099 COVID-19 patients hospitalized at 552 sites. The analysis of the data revealed that the average age of the affected population was 47 years[5]. Increased fatality cases were reported in older people, especially those with co-morbidities like diabetes mellitus, hyperlipidaemia, or an underlying cardiovascular disease[22]. This could probably be due to a weakened immune system in such individuals that may promote faster viral progression and infection establishment. This pattern of increased severity with age was also

noticed in the cases of SARS and MERS[13]. The hallmark of COVID-19, ARDS, may lead to respiratory failure, accounting for 70% of fatal COVID-19 cases. Additionally, cytokine storm and symptoms of sepsis may be the cause of death in 28% of COVID-19 cases[23].

3. IMMUNE RESPONSES INDUCED BY SARS-COV-2

The host's anti-viral immune response typically begins early during pathogenesis when the virus invades the host cell. However, the different immune evasion mechanisms adopted by SARS-CoV-2 ensure the successful establishment of an infection. More than 70% of the population is asymptomatic or present with only mild to moderate symptoms. Other individuals experience severe forms of the disease with a hyper-inflammation induced by a cytokine storm[2]. This difference in the immune response is perplexing, and studies are underway to understand this phenomenon.

3.1 Innate and Adaptive Immunity

The components of the innate immune system are activated upon the recognition of viral constituents and play a critical role in mediating viral clearance. The innate immune cells trigger a pro-inflammatory downstream pathway upon viral recognition. In a study, it was noted that the disease severity was correlated with cumulating inflammatory macrophages in bronchoalveolar lavage cells and a notable decrease in the alveolar macrophages[24]. However, future studies focusing on determining the inflammatory responses triggered upon SARS-CoV-2 infection in monocyte/macrophage lineage are needed.

In response to the extracellular pathogen, granulocytes degranulate to release toxic proteins. Macrophages mediate phagocytosis to remove the pathogens as well as the infected cells. Activated dendritic cells (DC) present antigens derived from pathogens to naïve T cells to trigger an adaptive immune response. Increased neutrophil profile was also noted in COVID-19 patients, and it is probable that it is linked with neutrophil extracellular traps (NET) and reactive oxygen species (ROS), which are anti-microbial mechanisms utilized by neutrophils. Inconsistent level of neutrophil-derived products could trigger cytokine storm, which is initiated by macrophages infiltrating lungs, that might lead to lung destruction [25]. In COVID-19 patients, decreased NK levels were

observed[26] similar to previously reported SARS cases[27]. Since NK cells mediate a variety of receptor expressions that either transduces the activation or inhibition signals, a cumulative of these signal outputs help in determining the functional role of NK cells including cytotoxicity and cytokine secretion. In SARS-CoV-2 individuals, NK group 2 member A (NKG2A), an NK inhibitory receptor level was markedly increased[26]. It works by binding to human leukocyte antigen, alpha chain E (HLA-E), which typically works by presenting the peptides derived from leader peptide sequences of class I HLA molecule. HLA-E-NKG2A complex triggers inhibitory signaling through two inhibition motifs based on tyrosine residue, thus limiting the cytokine production and cytotoxicity of the NK cells[28].

Additionally, one of the important innate immune mechanisms that reprogram the cells into an 'anti-viral' state is type 1 interferon (T1IFN). The expression of T1IFN and its downstream signals have a pivotal role in mitigating the infection and enhancing pathogen clearance by modulating cellular response[29]. The immune system uses pathogen-associated molecular patterns (PAMPs) to recognize the viral infection by sensing viral RNA. It then binds to endosomal RNA pattern recognition receptors (PRR), leading to the activation of Toll-like receptors (TLR3/7) and cytoplasmic RNA sensors like retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5). Typically, MDA5/RIG-I leads to the activation of interferon regulatory factor (IRF3), and the TLR3/7 aids in the nuclear translocation of NFκB. In turn, IRF3 increases the expression of T1IFN and NFκB aids in the making of pro-inflammatory cytokines like Tumor Necrosis Factor-Alpha (TNF-α), Interleukin (IL-6, IL-1) [30,31]. Following this, T1IFN and pro-inflammatory cytokines promote auto-amplification, where the interferon causes receptor activation (T1IFN) that results in the phosphorylation of signal transducer and activator of transcription (STAT) proteins, and the positive feedback cytokine expression happens in a loop through NFκB.

The shift from innate to adaptive mediated host immune responses is important for determining the COVID-19 severity. After the SARS-CoV-2 entry into cells, the viral antigenic peptides are presented by Class I Major Histocompatibility Complex (MHC) proteins to cluster of differentiation 8 (CD8⁺) cytotoxic T cells. Upon

activation, they exhibit clonal expansion and trigger virus-specific effector and memory T cells. CD8⁺ T_c cells initiate apoptosis of infected cells. Meanwhile, the virus and its constituent particles are recognized by antigen-presenting cells (APC), such as macrophages and dendritic cells and are presented to CD4⁺ T cells through MHC-II. Despite a wave of information available on the MHC polymorphisms and its susceptibility to SARS-CoV[32–34], very little is known about its association with SARS-CoV-2 infection. Further studies are warranted as they can show beneficiary aspects for personalized medicine that could be used in the treatment of COVID-19.

3.2 Humoral Mediated Immunity

A study conducted on 67 SARS patients, found higher levels of immunoglobulin M (IgM) than immunoglobulin G (IgG) against SARS-CoV in the initial days. By the end of week 25, a gradual decrease in IgM and a sharp increase in IgG levels were noted[35]. Similarly, several studies have reported elevated IgM and IgG levels in the first few weeks of clinical manifestations, followed by a steep decline, yet detectable levels of IgM (compared to IgG levels) during infection by SARS-CoV and MERS-CoV[36,37]. Another study found detectable base IgM levels on day 7 and heightened levels on day 28 when analyzed in 28 patients. However, IgG appeared only on day 10, peaking by day 49 as analyzed in 45 patients[38]. In a study conducted on SARS survivors, post 6 years, it was noticed that anti-SARS-CoV antibody levels were infinitesimal in 21 of 23 individuals and no one exhibited specific memory B cell. On the other hand, in 14 of 23 individuals, specific memory T cells were observed[39]. The dynamics of SARS-CoV-2 antibody profile is yet to be conclusively studied and is currently under investigation. While it is early to identify the anti-SARS-CoV-2 antibody response pattern, preliminary studies have identified a change in the levels of IgG and IgM.

Of the various structural and non-structural proteins (NSP) encoded by SARS-CoV-2, the most immunogenic antigens are nucleoprotein (N) and S proteins. Detectable level of antibodies against N proteins is the first to appear whereas the antibodies against S proteins appear at a later stage and tend to bind to the viral envelope. A study was conducted to evaluate the early antibody profile against nucleocapsid (NP) in SARS-CoV-2 individuals. IgM, IgA, and IgG plasma levels were detected in 90.4%, 93.3% and 77.9% respectively among 208 individuals.

The median time for the IgM and IgA detection was 5 days post-symptom onset (PSO) and 14 days PSO for IgG[40].

3.3 Immune Evasion Strategies

Research studies on the SARS-CoV-2 immune evasion mechanisms are still in its infancy. Current observations indicate that CoVs evade immune detection and inhibit the host immune responses. This partly explains the increased incubation period for

SARS-CoV-2, typically 11 days on average as compared to influenza, 4 days [41]. During the early stage of infection, owing to their immune evasion property, they efficiently escape the host immune system. Since SARS-CoV-2 is also a member of the *Betacoronavirus* genus, extrapolation of knowledge on the strategies of SARS-CoV and MERS-CoV to circumvent the host surveillance system will possibly help understand the mechanisms underlying immune evasion of SARS-CoV-2.

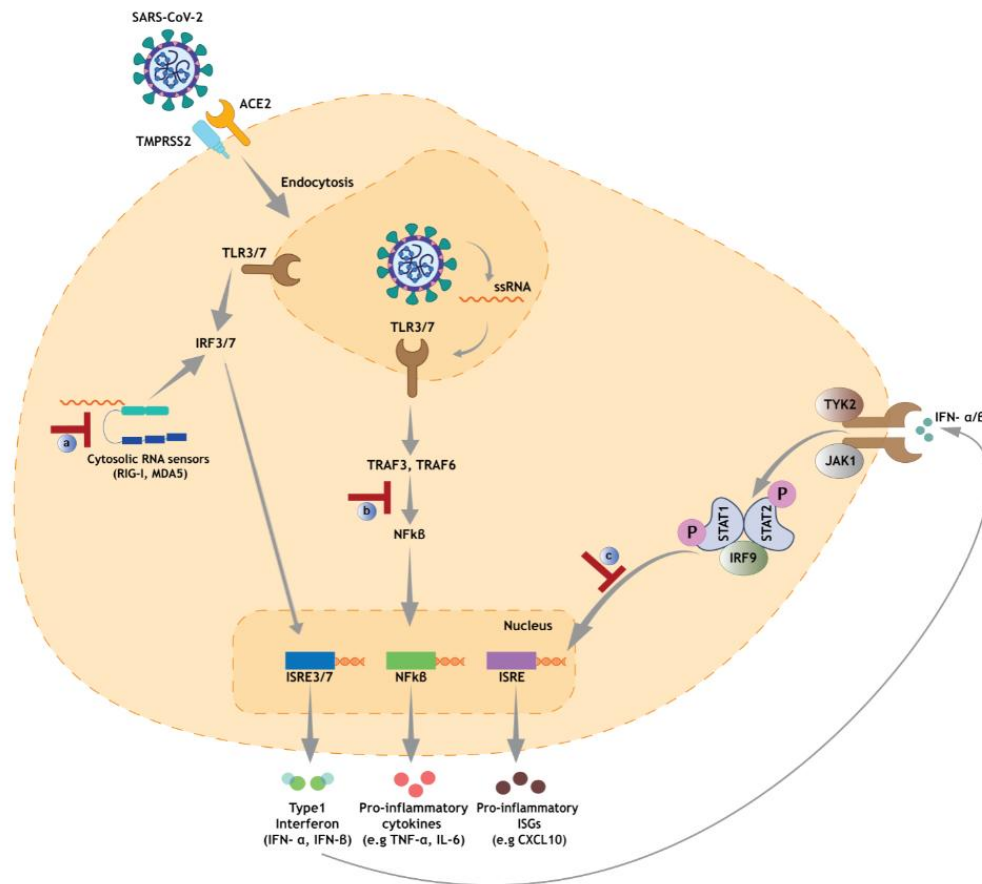


Fig. 2. Potential immune evasion strategy of SARS-CoV-2 by impeding T1IFN: The virus enters inside the host cell through the interaction of spike surface glycoprotein with ACE2 receptor on the cell surface. While, the RNA virus typically triggers the TLR3/7 in endosomes and RIG-1, MDA5, in the cytoplasm, (a) SARS-CoV-2 might interfere with the cytosolic RNA sensors which restrict the activation of IRF3/7, thereby suppressing the production of Type 1 interferons. (b) Additionally, SARS-CoV-2 may also impede the TRAF 3/6 activation, which limits the activation of NFκB thereby suppressing pro-inflammatory cytokine production (IL-1, IL-6, TNF-α). (c) Furthermore, novel CoV can also inhibit the STAT transcription factor activation downstream of IFN/IFNAR, which further limits the anti-viral immune response. Overall, these inhibition checkpoints shall prohibit the containment of the virus-mediated by the recruitment of the host immune cells and the activation of anti-viral strategy

In a majority of the infected individuals, SARS-CoV-2 most likely evades the immune response by primarily inhibiting the type I interferon signaling mechanism (Fig. 2), or by inhibiting the TNF receptor-associated factors (TRAF) which is crucial for inducing the IRF-3/7, NF κ B, RIG5, and MDA5 ligation[42]. The viral proteins including envelope membrane (E) and NSPs (NS4a, NS4b, NS15) are the central molecules that play a crucial role in modulating the immune responses. On analysis of two MERS-CoV individuals with different severity showed that type I interferon response is remarkably lower in poor outcome (death) individual rather than in convalescent patients[43]. In case of the adaptive immune responses, antigen presentation by class-I and class-II MHC molecules were downregulated when MERS-CoV infected antigen presenting cells, macrophages, and DC, which resulted in markedly diminished T cell activation[44].

In addition, CoVs form a double vesicle, to avoid being detected by cytosolic PRRs[19]. Additionally, the virus uses non-structural proteins to evade the immune response by inhibiting the interferon (IFN). For example, NSP1 of SARS-CoV inhibits T1INF by RNA-host degradation, host translation machinery inactivation, and inhibiting the phosphorylation of STAT proteins. This mechanism could deregulate T1INF signaling to disseminate the virus thereby leading to increased disease severity[25,45]. Since the RNA viral genome of SARS-CoV is 5' capless, viral recognition followed by triggering host immune response happens. To get around this, NSP14 initiates cap formation along with NSP16 so the viral RNA resembles similar to the host cell RNA thereby evading the PRR recognition[45]. In addition, SARS-CoV could also utilize protein accessories to evade the immune response. For example, the gene segment in open reading frame3b (ORF3b) has the ability to antagonize IFN pathway thereby limiting the effector cell activation[46].

4. POTENTIAL ROLE OF ADE IN SARS-COV-2 INFECTION

Numerous research studies have suggested that pre-existing antibodies from prior infection by other CoVs, such as a common cold, may facilitate the entry of different serotype inside the host cell, hence promoting the chances of increased severity. This mechanism is termed as ADE where the antibodies elicited by an infection of one particular viral serotype atypically promote

the viral replication and exuberate the immune response upon exposure to a new viral serotype. This type of observation was initially seen in dengue viruses (DENV), where the cross-reactive antibodies generated to a specific DENV serotype, predisposes to an enhanced illness that may contribute to the development of dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) upon a different DENV serotype mediated infection[47]. Interestingly, IgG antibodies against a particular DENV serotype may cross the placenta to reach the fetus that may result in a detrimental immune response against other serotypes after birth. Additionally, children having passive immunity from immunized mothers may exhibit DHF upon first infection[48].

Reasons why some people can mount immune responses more quickly than others against SARS-CoV-2 are unknown. It has been suggested that priming effects from anti-CoV antibodies against SARS-CoV-2 infection might be a possible explanation for severe clinical manifestations. Some preliminary studies have reported cross-reactivity of spike protein from SARS-CoV-2 and SARS-CoV, where the outcome has rarely seemed to be cross-neutralizing [49]. In terms of MERS, a possible mechanism based on ADE has been postulated. The viral entry into the cell is mediated by the complex formed by neutralizing antibodies (nAb) generated against the Receptor binding domain (RBD) of S protein of MERS-CoV with the Fc receptor. This complex (nAb-Fc) would mimic the virus-cell surface receptor and facilitates its entry into the IgG Fc receptor-expressing cells. If such a mechanism is followed by SARS-CoV-2, the ideology of blocking the viral entry by using nAbs against S protein would have the opposite effect. Rather than blocking the viral entry, the cell infection will be facilitated followed by an accelerated increase in the number of infected cell types[50]. In line with the above mechanism, studies have also shown that pathways other than ACE2 also mediate viral entry of SARS-CoV into the cell. In a study, it was demonstrated *in-vitro* that while anti-spike antibodies mostly prevented the viral entry in certain cells, they facilitated infection by highly replicating SARS-CoV. This infection was found to be mediated by fragment crystallizable gamma chain receptor (Fc- γ -RII) and not the usual endosomal/lysosomal pathway of ACE2[51]. This was also confirmed in a human promonocyte cell line (HL-CZ) that expresses both ACE2 and Fc- γ -RII. Additionally, when a high concentration of

anti-SARS-CoV sera from patients was added, apart from inhibiting the viral replication, an enhanced level of apoptosis was also noted.

Different subclasses of IgG exhibit varied affinity to different Fc-γR resulting in a differential immune response. Experimental results on SARS-CoV suggest Fc-γ-RIIa and Fc-γ-RIIb, and not Fc-γ-RIII and Fc-γ-RI in aiding ADE mechanism[52]. Additionally, polymorphisms in Fc-γ-RIIa correlated with varying SARS-CoV severity. For example, allelic polymorphism in G or A nucleotide resulted in arginine or histidine at residue 131 of the Ig binding domain of Fc-γ-RIIa. This resulted in varied receptor affinity and specificity to the binding of IgG subclasses[53]. Among the several factors that determine the susceptibility to COVID-19 severity, the individual composition of the cellular expression of the polymorphisms in Fc-γ-RII can play a crucial role. Altogether, the speculated ADE mechanism should be taken into consideration while developing therapeutics for COVID-19.

5. CYTOKINE STORM IN SARS-COV-2 INFECTION

A marked characteristic of infection by SARS-CoV-2 is a 'cytokine storm' where a heightened inflammatory response induces the production of a massive amount of pro-inflammatory cytokines.

Multiple studies analyzing the cytokine profile have indicated a direct correlation between multiple-organ failure, lung injury, and severe clinical manifestations of COVID-19 with elevated cytokine levels[54–57]. Innate immune cells like macrophages and mast cells are the major sources of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α). The cytokine storm is initiated by a markedly increased count in the number of pro-inflammatory cytokine production in circulation. Following this, heightened recruitment of various immune cells like T cells, macrophages, and neutrophils circulate to the infection site leaving a devastating impact on the tissues obtained from capillary and alveolar damage, leading to multiple organ failure and eventually death[58]. Previous reports of a cytokine storm are noticed in viral infections including the H1N1 virus, H5N1 virus, SARS-CoV, MERS-CoV. Elevated levels of both anti-inflammatory (IL-10) and pro-inflammatory (IL-1, IL-6) cytokine profiles were observed in the serum of cytokine storm individuals. Without appropriate therapeutic intervention, this can result in multi-organ failure followed by death.

According to a report, lymphopenia, thrombopenia, hypoalbuminemia, hyperfibrinogenemia, and increased levels of C-Reactive Protein (CRP), IL-6, Monocyte Chemoattractant protein-1 (CCL2), C-X-C motif

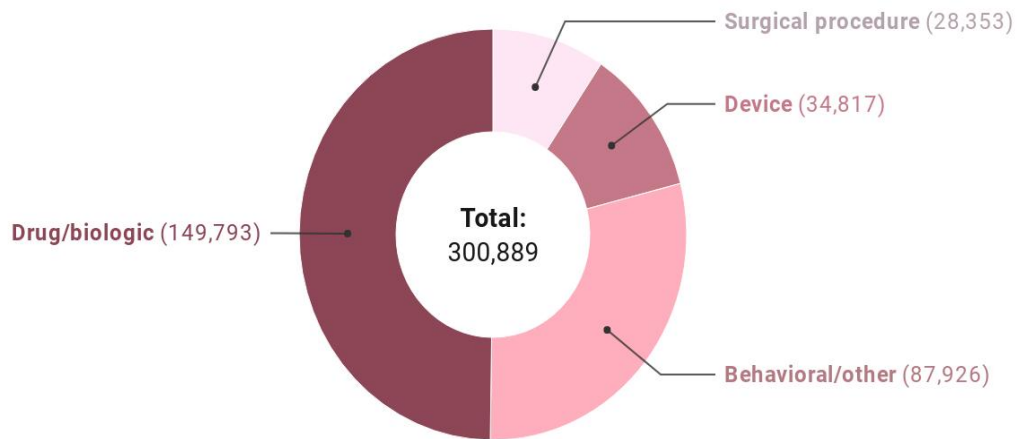


Fig. 3. Different categories of clinical intervention for COVID-19. The number of recorded studies (on June 25, 2020) under each category is displayed, with the major proportion of clinical trials being for drugs. (Data source: ClinicalTrials.gov)

chemokine 10 (CXCL10), and TNF- α are predictive markers of cytokine storm[59]. Heightened levels of cytokines can trigger ARDS, followed by multiple organ failure mostly resulting in death in critically ill COVID-19 patients. Early reports have also suggested ARDS as a hallmark of the clinical consequence of SARS-CoV-2 as it accounts for a significant number of deaths among infected individuals[60]. Several studies are currently trying to understand hyper inflammation or the key inflammatory mediators that underlie cytokine storm in COVID-19 patients.

6. TREATMENT OPTIONS FOR COVID-19

Due to an alarming rise in the cases of COVID-19 and death tolls globally, there is an immediate need for an effective therapeutic intervention (Fig. 3). At present, there is no one established anti-viral drug or recommended vaccine for COVID-19, although several vaccine candidates are currently under clinical trials to test their various clinical parameters like efficacy and safety profile. Hence, the following section should not be misinterpreted as a proof-of-concept based treatment recommendation, but should be viewed as extrapolated data from other related conditions for providing insights into anecdotal evidence of experimental treatment.

6.1 Anti-viral Treatment

6.1.1 Azithromycin

Azithromycin is a weak base, which gained widespread recognition in the management of COVID-19. It exhibits a mechanism of action similar to that of hydroxychloroquine. Of note, hydroxychloroquine has been dropped out of the COVID-19 clinical studies as it did not reduce the mortality index and was unlikely to be effective in treating the disease. Apart from being anti-microbial, the immunomodulatory property of azithromycin helps distinctly in the treatment of chronic pulmonary disorders. Azithromycin regulates the macrophage conversion to anti-inflammatory M2 phenotype and also inhibits the transcription factor STAT and the NF κ B signaling pathway[61]. The anti-inflammatory effect of this drug is of particular interest in treating the non-COVID-19 related ARDS patients, where a drastic reduction in mortality index and extubation time period was noted[62]. However, azithromycin, similar to hydroxychloroquine, has been associated with a prolonged QT interval and an increased risk for cardiac arrest and

tachyarrhythmias. Therefore, close monitoring of the patient's electrolyte and fluid status, and electrocardiogram (ECG), along with an assessment of pharmacokinetics is crucial when administering azithromycin to a severely ill COVID-19 patient[63].

6.1.2 Remdesivir

Remdesivir is a nucleoside analog, a prodrug to adenosine, which was initially developed to treat Ebola and Marburg fever. While the drug did not exhibit the expected efficacy in the human clinical trials for these diseases, it demonstrated a surprising efficacy against SARS-CoV and MERS-CoV[64]. For this reason, remdesivir is being majorly explored for its potential as a prophylactic drug for SARS-CoV-2. The drug competes with ATP by replacing the nucleoside adenosine during the synthesis of RNA, inhibiting RNA dependent RNA polymerase (RdRP) in the process[65]. The RdRP of SARS-CoV-2 was found to have a structural similarity of 96% with SARS-CoV, rendering them a potential candidate against COVID-19. During the early days of the outbreak, remdesivir was subjected to *in-vitro* testing against SARS-CoV-2 at the Wuhan Virus Research Institute. The findings reported an inhibition in the establishment of viral infection in cell culture at concentration levels (effective concentration [EC50] = 0.77 μ M and cytotoxic concentration [CC50] > 100 μ M) that can be potentially met at *in-vivo* studies. In a case study, a 40-year old male tested positive for COVID-19 with co-morbidities such as obesity, anxiety, showed a significant improvement upon late initiation of remdesivir antiviral therapy[66]. However, studies on large scale will help determine the efficacy of the drug against SARS-CoV-2 and clinical trials are currently underway in Europe and other countries. On the contrary, in a randomized, double-blind, placebo-controlled, multi-center trial conducted on adults with severe COVID-19 revealed no signs of improvement in clinical manifestations, mortality index and viral clearance time[67]. A promising result for this drug is anticipated, if it causes a drastic reduction in the pulmonary viral load and an acceptable efficacy profile in COVID-19 cases.

6.1.3 Lopinavir/ritonavir (LPV/r)

Protease inhibitors have long been recognized for their potential to inhibit viral replication, as they interrupt the cleaving of structural proteins from precursor polypeptides that facilitate the

maturation to a virion particle. A combination of two protease inhibitors, LPV/r or better known by the commercial names 'Kaletra' and 'Aluvia' is widely used for the treatment of human immunodeficiency virus (HIV) and are considered to be potential candidates for the treatment of COVID-19. In the LPV/r combination, ritonavir inhibits the CYP3A4 activation and drug metabolism, thereby improving the bioavailability of LPV[68]. Some preliminary studies have found evidence for the effectiveness of LPV/r against other CoVs. In SARS, a combination of LPV/r has significantly reduced the risk of complications like ARDS and death as opposed to the use of ritonavir alone[69]. Such type of results were also noted in a retrospective study conducted in 1000 SARS patients, where LPV/r drastically reduced the mortality risk rate and the extubation time[70]. In another study, two randomized clinical trials assessing the potential of LPV/r in COVID-19 patients were conducted. The study noted recurrent gastrointestinal side effects in patients receiving LPV/r treatment. However, both of these studies had severe limitations in terms of study design and the use of a small cohort. Currently, there is no established scientific evidence supporting the use of LPV/r for COVID-19, and WHO has announced the drugs lopinavir/ritonavir, ivermectin, and hydroxychloroquine to be ineffective in combating the SARS-CoV-2 infection.

6.1.4 Favipiravir

Favipiravir (FPV), a prodrug, is an RdRp inhibitor, which has been demonstrated to be effective in the treatment of Ebola and Influenza virus. Owing to the lack of established evidence and increased time needed for developing novel therapeutic interventions for COVID-19, the option of repurposing the existing pharmaceutical drugs are being explored. In an observational study conducted in Shenzhen, rapid viral clearance (approximately 4 days) and an increased recovery rate (71.4%) in non-critical COVID-19 patients were observed upon the use of FPV[71]. Another study summarized the safety profile of FPV extracted from six phase II/III controlled studies. Interestingly, the drug demonstrated a lower proportion of grade 1-4 adverse effects and gastrointestinal effects than the comparators. In an open-label controlled study, upon the use of FPV, early viral clearance, and improved chest computerized tomography (CT) imaging were found by day 14[72]. These findings suggested that the FPV aids in

controlling the disease progression of COVID-19 by inhibiting the SARS-CoV-2. Recently, this antiviral drug showed rapid viral clearance, better radiological imaging, and significant clinical improvements in about 88% mild to moderate COVID-19 individuals. Hence, FPV or better known by the commercial name (FabliFlu) is currently used for the treatment of mild-moderate COVID-19 cases in India after the approval from the drug controller general of India (DCGI).

6.1.5 COVID-19 candidate vaccines in the clinical evaluation

As of 20th August 2020, thirty candidates are currently under clinical trial, including Ad5-nCoV from CanSino Biologicals, mRNA-1273 from Moderna, ChAdOx1-S from University of Oxford/AstraZeneca, INO-4800 from Inovio, and NVX-CoV2373 from Novavax (Table 1). There are 139 additional candidate vaccines under preclinical evaluation as per the draft landscape document prepared by WHO[73].

A brief description of the vaccine development and its clinical study outcomes are portrayed. As of 20th August, 2020, approximately 139 candidate vaccines are under pre-clinical evaluation studies (Data source: WHO Draft landscape of candidate vaccines currently under clinical investigation)[73].

6.1.6 Immunological approaches for the treatment of COVID-19

Considering the hyperactive inflammation effects of SARS-CoV-2 infection, the option of agents that modulate the immune response are being explored as a potential treatment for the management of moderate- severe cases of COVID-19. The following section explains some of the immune-based therapies.

6.1.7 Neutralizing antibodies against SARS-CoV-2

The approach of using polyclonal antibodies from SARS-CoV-2 convalescent patients for treating the SARS-CoV-2 infection is being explored. Currently, there are no SARS-CoV-2 specific neutralizing monoclonal antibodies (mAbs) being reported. Owing to the high sequence identity of S protein between SARS-CoV-2 and SARS-CoV[74], researchers have attempted to test the potential cross-reactivity and/or cross-neutralizing activity of SARS-CoV nAbs against

Table 1. The table outlines some of the vaccine candidates under clinical trial investigation

Candidate vaccine	Developer	Description and study details	Current stage of clinical trial
mRNA-1273	Moderna/NIAID	mRNA-1273 is a novel vaccine encapsulated in a lipid nanoparticle (LNP) that encodes for a full-length spike (S) protein of SARS-CoV-2. Based on Phase I clinical study led by the National Institute of Allergy and Infectious Diseases (NIAID), positive interim clinical data for the vaccine was announced (NCT04283461). Currently, a phase 2a, randomized, placebo controlled study is ongoing to determine safety, immunogenicity, and other clinical parameters (NCT04405076). Based on the feedback received from the U.S. Food and Drug Administration (FDA), phase III clinical trial protocol has been finalized and is expected to enrol 30,000 participants (NCT04470427).	Phase III
Ad5-nCoV	Beijing Institute of Biotechnology and CanSino Biologics Inc.	Ad5-nCoV is a replication faulty Ad5 vectored vaccine that expresses the S protein of SARS-CoV-2. A non-randomized, single-center, dose-escalating phase I clinical study was conducted in 108 participants. The vaccine was immunogenic as well as capable of inducing T-cell and humoral mediated responses in most individuals. On a single dose administration, a 4-fold increase in the binding antibodies to RBD (in 94-100% of participants) and a 4-fold increase in nAb to live virus (in 50-75% of participants) was noted (ChiCTR2000030906). A phase II, double blind, randomized, placebo-controlled study was conducted to determine the clinical parameters such as immunogenicity and the safety profile. The findings revealed the vaccine at 5×10^{10} viral particles to be safe and it induced a heightened immune response upon single-dose administration (NCT04341389).	Phase II
INO-4800	Inovio Pharmaceuticals	INO-4800 is a DNA candidate vaccine that delivers DNA into cells, which is converted to the protein that triggers the immune system to generate robust T cells and antibody production. CELLECTRA® 2000 causes electroporation that allows the plasmids to enter and start replicating, thereby boosting the immune system further. The vaccine is currently enrolled for Phase I/II clinical evaluation to evaluate the safety, tolerability, and immunogenicity profile (NCT04447781).	Phase I/II
ChAdOx1-S	University of Oxford /AstraZeneca	To the ChAdOx1 construct, the genetic material is added that expresses the spike protein of SARS-CoV-2. Following the vaccination, the spike protein is released, priming the immune system to attack the coronavirus if it tries to establish an infection. Currently, Phase II/III clinical trials are underway in more than 10,000 individuals to assess the safety, efficacy, and immunogenicity properties (2020-001228-32).	Phase II/III
NVX-CoV2373	Novavax	NVX-CoV2373 is a perfusion protein created using proprietary nanoparticle technology. An adjuvant, Matrix-M, is conjugated to trigger a heightened immune response and stimulate the neutralizing antibody production. Preclinical studies have reported high immunogenicity and high levels of neutralizing antibodies. Phase I/II randomized, observer-blinded clinical trial is ongoing in 130 healthy adults, and the study is estimated to be completed by July 2021 (NCT04368988).	Phase I/II

SARS-CoV-2. It should be noted that SARS-CoV RBD specific neutralizing mAb, CR3022, has a higher binding affinity to the RBD domain of the SARS-CoV-2, and was able to recognize an epitope on RBD other than the ACE-2 binding domain[75]. Additionally, sera from recovered SARS patients specific for the SARS-CoV S1 subunit, can have a cross-neutralizing property and prevent the SARS-CoV-2 infection mediated by S protein[6]. In human embryonic kidney 293 cells (HEK293T) expressing the human ACE2 receptor, it was noted that SARS-CoV RBD specific polyclonal Abs cross-reacted with SARS-CoV-2 RBD protein thereby cross-neutralizing the infection by SARS-CoV-2. Hence the possibility of SARS-CoV-RBD based vaccines to prevent/control the SARS-CoV-2 infection is under investigation[76].

6.1.8 Targeting the pro-inflammatory cytokines in the cytokine storm

Understanding the mechanism(s) underlying cytokine storm in COVID-19 patients will help in the development of new therapeutic interventions. Since the cytokine profile pattern differs based on the severity of the disease, their evaluation is of utmost importance before the administration of immunosuppressive drugs. In the case of Intensive Care Unit (ICU) patients, higher levels of IL-2, granulocyte colony-stimulating factor (G-CSF), IL-10, monocyte chemoattractant protein-1 (MCP-1) (CCL-2), IL-7, TNF, and MIP-1A (CCL-3) were noted when compared to non-ICU individuals[5]. Additionally, in the critically ill COVID-19 patients, elevated levels of several cytokines and chemokines like IL-6, IL-10, interferon gamma induce protein 10 (IP-10) were reported[77]. Among the several cytokines, IL-6 has gained considerable attention and their receptor antagonist 'tocilizumab' and 'sarilumab' are under the clinical trials as vaccine candidates for COVID-19.

'Anakinra', a recombinant IL-1 antagonist was developed to control the cytokine storm and its associated tissue damage in individuals with sepsis. This drug is suspected to have the potential to reduce hyper-inflammation in severe COVID-19 cases and is currently being explored in a randomized, placebo-controlled study in children and adults experiencing MAS (NCT02780583)[78].

6.1.9 Inhibition of janus kinases

Janus Kinases (JAK) is an important component in the signaling of IL-6, T1IFN, and T2IFN

receptors. They phosphorylate STAT, a protein that influences the production of pro-inflammatory cytokines. When JAK is inhibited, cytokine expression may possibly be limited, reducing the cytokine storm in COVID-19 patients. However, JAK also centrally expresses T1IFN, which plays a vital role in reducing viral replication and initiating pathogen clearance[79]. As an evasion mechanism, SARS-CoV-2 has been shown to inhibit T1IFN to promote viral replication during the initial stages of the infection. Therefore, the use of JAK inhibitors would facilitate further suppression of T1IFN, thereby limiting pathogen clearance. However, there are at least two clinical studies underway to determine the safety, efficacy, and other parameters for JAK inhibitors in severe COVID-19 patients (NCT04338958).

6.1.10 Convalescent plasma

Convalescent plasma has been used as a mode of treatment for various infections and is currently being explored for COVID-19. Researchers believe this treatment can be considered for severe cases as it helps to boost the immunity against the virus. In an open-label study with 103 COVID-19 positive individuals, convalescent plasma showed little to no effect within 28 days[80]. On the contrary, a meta-analysis of 15-controlled studies exhibited a drastic improvement in the mortality index upon convalescent plasma treatment. However, all these studies were mostly of very low quality with moderate-high risk bias[81]. Currently, convalescent plasma is given to severe/critically ill COVID-19 patients in some regions; however larger studies are needed to test the safety and clinical efficacy.

7. CONCLUSION

The ongoing COVID-19 pandemic caused by the novel SARS-CoV-2 coronavirus has a devastating impact on the global population and is therefore an emergency public health concern. The virus has the capacity to spread undetected within the susceptible population, making the outbreak one of the deadliest pandemics since the Spanish Influenza of 1918. As we are only beginning to understand the host's anti-viral immune response against SARS-CoV-2, future studies focusing on understanding its correlation to the degree of disease severity may provide important insights for developing effective therapeutics against COVID-19. Additionally, unraveling the cell- and tissue-specific host

factors influencing the pathology will aid in designing disease-stage specific therapeutics to mitigate the viral replication and curtail the inflammatory damage. Owing to growing evidence on the connection between MHC polymorphisms and susceptibility to SARS-CoV-2, further studies focusing on factors that determine the individual susceptibility to COVID-19 are warranted. Although there are several vaccine candidates under clinical investigation, there is currently no established anti-viral drug or recommended vaccine for COVID-19. Therefore, preventive measures like social distancing and movement restriction may be the only way to curb the upsurge and control the spread of COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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