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Recent Advances in Understanding Covid-19 Pathophysiology and Therapy: A Review

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Abstract

For over two years, the global COVID-19 pandemic has persisted, and its continuation is anticipated. The emergence and rapid spread of numerous new virus variations across continents have been observed. These variants, differing from previously known strains, manifest a spectrum of behaviors and clinical presentations, ranging from asymptomatic cases to severe illnesses and fatalities. Despite substantial research efforts in recent years, significant uncertainties persist in understanding the disease, encompassing variations in clinical outcomes, comorbidities, and challenges faced by individuals infected with COVID-19. Beyond the acute phase of infection, the prevalence of post-COVID-19 symptoms, often denoted as "long COVID," is notable, particularly in individuals recovering from the disease. Nevertheless, a research gap persists concerning the pathophysiological mechanisms underlying newly emerging viral variant infections, post-COVID-19 conditions, and the corresponding therapeutic strategies. This review is presented to analyze recent advancements in comprehending the pathophysiology and therapy of COVID-19.

Keywords: *COVID 19; recent advances; pathophysiology; therapy.*

Introduction

The onset of the COVID-19 pandemic in December 2019, marked by the diagnosis of patients in Wuhan, China with an atypical pneumonia, is on the brink of entering its fourth year. This event signifies the third major coronavirus outbreak, with the prior Middle East respiratory disease (MERS) and severe acute respiratory syndrome (SARS) viruses being contained before causing global pandemics. The ongoing evolution of SARS-CoV-2 has historically detrimentally impacted both global public health and the economy. By July 2023, the global tally of confirmed COVID-19 cases reached almost 767 million, resulting in nearly 6.95 mil-lion fatalities. Beyond acute illness and mortality, the pandemic has ad-versely affected psychological well-being, economic stability, and access to healthcare for other conditions, contributing to increased fatalities from additional medical complications. Moreover, the virus's rapid mutation and distribution have led to the emergence of various strains, including Alpha, Beta, Gamma, Delta, and Omicron, with heightened infectivity observed in several variants. Despite substantial research efforts, nu-merous unresolved issues persist regarding the disease, encompassing variations in clinical outcomes, comorbidities, and challenges faced by those infected. Notably, the prevalence of post-COVID-19 symptoms, known as "long COVID," remains a global concern. Yet, a notable research gap exists concerning the

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pathophysiological mechanisms of emerging viral variants, post-COVID-19 conditions, and corresponding therapeutic strategies. Consequently, this review is presented to analyze recent de-velopments in comprehending the pathophysiology and therapy of COVID-19.

Pathophysiology and Pathogenesis

Interactions and entry of the SARS-CoV-2 into the cell

The main source of new infections is asymptomatic carriers and con-firmed COVID-19 patients (16). It has been hypothesised that infection can occur via the fecal-oral pathway in addition to respiratory droplets and interaction with surfaces that are contaminated.[33-35] The viral spike (S) protein, which interacts to the angiotensin-converting enzyme 2 (ACE2) receptor when SARS-CoV-2 first infects humans, facilitates the virus's en-trance into host cells like pneumocytes, bronchial epithelial cells, and nasal cells. The S protein of SARS-CoV-2 exhibits a binding affinity with ACE2 that is 10-20 times greater than that of SARS-CoV, which could account for the rapid spread of the pandemic. [36-38]

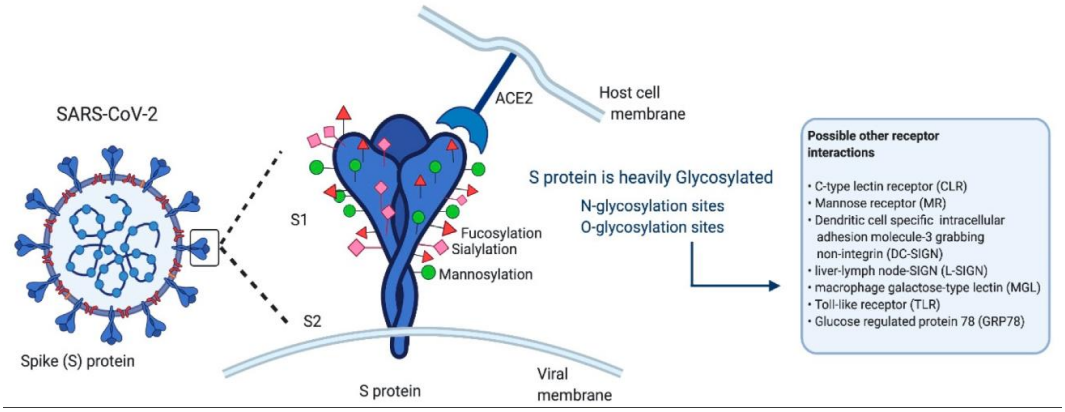

Figure 1. Schematic representation of SARS-CoV-2 virus showing the Spike (S) protein which is heavily glycosylated (O-glycosylation and N-glycosylation) with numerous fucose, mannose and sialyl residues. These sugar moieties have the potential to bind to C-lectin type receptors (CLR), mannose receptor (MR), dendritic cell-specific intracellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), homologue dendritic cell-specific intercellular adhesion mole-cule-3-grabbing nonintegrin related (L-SIGN), macrophage galactose-type lectin (MGL), toll-like receptors (TLR), and glucose regulated protein 78 (GRP78).

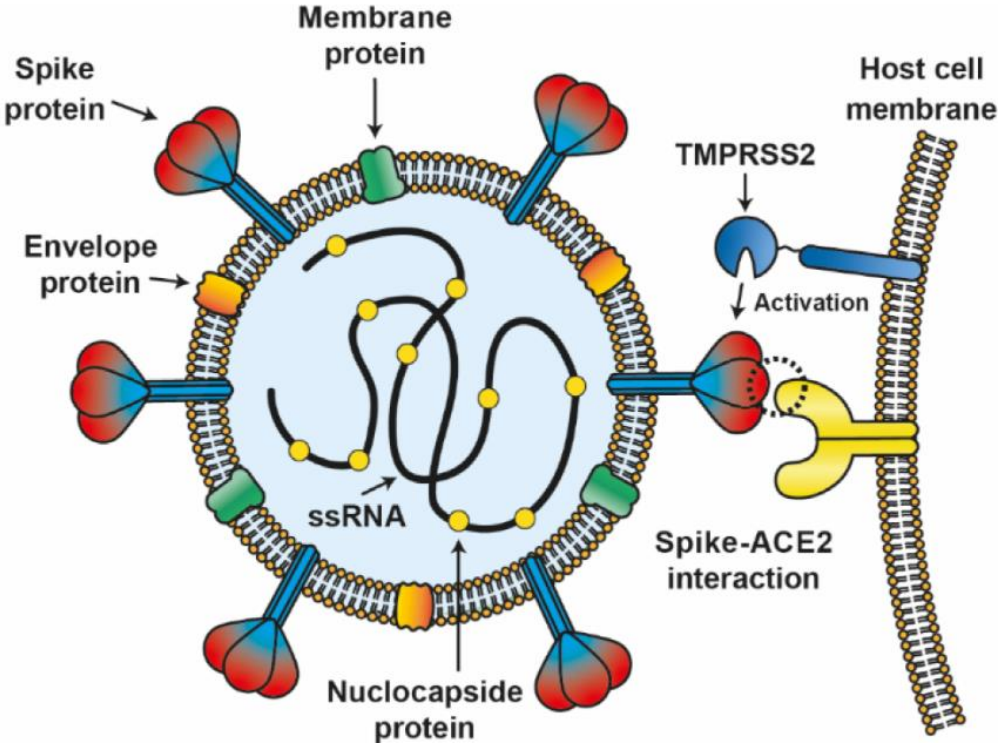

Figure 2. Interaction between SARS-CoV-2 and host cell. The SARS-CoV-2 virion is composed of 4 structural proteins, spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N), associated with single-stranded RNA (ssRNA) of the virion. S protein interacts with the host cell ACE2 protein and is activated by TMPRSS2 as part of the infection mechanism.

Long COVID

Even while extended COVID-19 is quite prevalent, little is known about the fundamental pathophysiology's mechanisms. A number of the-ories have been put forth to explain the pathophysiology of long-term COVID-19.[65-66] These include the following: dysfunctional neurological signalling, imbalance in microbiome in the gastrointestinal tract, rein-statement of secondary infectious agents (e.g., EBV, HHV-6, HCMV, VZV, etc.), immune system disruption, long-term exposure of SARS-CoV-2 in tissues, endothelial irregularities in microvascular clotting of the blood, autoimmunity along with immune priming from molecular mim-icry, among others.[67,68] More research has revealed that two thirds of people with long-term COVID are linked to a number of possible risk factors and diseases, such as type 2 diabetes, female sex, underpinning viral reactivation, the existence of particular autoantibodies, along with disorders of connective tissue. There have been reports of a higher inci-dence of long COVID-19 in several ethnic groups, such as those who identify as Latino or Hispanic. Long COVID-19, which is associated to diminished income and lack of adequate rest in preliminary weeks fol-lowing SARS-CoV-2 infection, characterised by neurological symptoms, gastrointestinal symptoms, cognitive impairment, brain fog, incomplete sleep, fatigue, pain, postural orthostatic tachycardia syn-drome post-exertional and malaise and other symptoms. (69,70)

RECENT ADVANCES IN PATHOPHYSIOLOGY OF COVID -19

Role of Soluble PD-L1 in the Course of Severe and Non-Severe COVID-19

After discovering that high levels of sPD-L1 corresponded with low lymphocyte counts and high CRP levels, as well as longer hospital length of stay (LOS) and death, Sabbatino, F.'s study suggested sPD-L1 as a useful prognostic biomarker for COVID-19. Moreover, SARS-CoV-2-infected ep-ithelial cells showed an increase of sPD-L1 [20].

sPD-L1 overexpression was observed in COVID-19 patients who needed invasive mechanical breathing, according to another observational investigation [21]. It was determined that although sPD-L1 stimulates an immune escape during the early stages of COVID-19, it may also function to reduce an overabundance of an immune response later on, demonstrating its significance in COVID-19 prognosis.34-45

Molecular Dynamics Simulations Suggest SARS-CoV-2 3CLpro Muta-tions in Beta and Omicron Variants Do Not Alter Binding Affinities for Cleavage Sites of Non-Structural Proteins

De Freitas Amorim et al. found that Gly143 and Glu166 are important residues in substrate recognition based on hydrogen bonding investiga-tions, indicating that these residues may be included as pharmacophoric centres for Beta and Omicron variations in drug design. Based on our findings, Gly143 and Glu166 may be broad-spectrum pharmacophoric centres of SARS-CoV-2 3CLpro since they are necessary residues to interact with Gln6 of the various substrates.41-46

Growth Arrest of Alveolar Cells in Response to Cytokines from Spike S1-Activated Macrophages: Role of IFN-γ

The symptoms of acute respiratory distress syndrome (ARDS) include high-permeability pulmonary edoema and severe hypoxemia.Along with these changes, there is an increase in the amount of amino acids inside the cell, which is probably related to the activation of protein degradation, as well as a blockade of protein synthesis and the activation of autophagy. Owing to an increased secretion of IFN-γ in the conditioned medium by S1-activated macrophages, these alterations are correlated with the in-duction of IFN-regulatory factor 1 (IRF-1). When baricitinib is added, the effects that are seen are avoided. Finally, our results imply that the alveolar epithelial damage seen in COVID-19-related ARDS may be related to the IFN-γ-IRF-1 signalling pathway.47-51

Molecular Dynamics Simulations Suggest SARS-CoV-2 3CLpro Muta-tions in Beta and Omicron Variants Do Not Alter Binding Affinities for Cleavage Sites of Non-Structural Proteins

The 3CL or nsp5 protease, the most significant viral protease needed for the maturation of viral proteins during host infection, is essential to the course of the SARS-CoV-2 infection. Here, 3CLproWT, 3CLproH41A, 3CLproBeta, and 3CLproOmicron were simulated for 500 ns in complex with the substrates nsp 4|5 and nsp 5|6 by de Freitas Amorim et al. De Freitas Amorim et al. demonstrate that neither conformational changes nor alterations in substrate binding affinities were significantly caused by mutations in the 3CLpro found in the SARS-CoV-2 variants of concern (VOCs). Nonetheless, 3CLproBeta and 3CLproOmicron showed noticea-bly high cleavage rates at the nsp4–nsp5 boundary, which may be crucial for viral fitness gain and replication.. Based on our findings, Gly143 and Glu166 may be broad-spectrum pharmacophoric centres of SARS since they are necessary residues to interact with Gln6 of the various sub-strates.-CoV-2 3CLpro.52-56

S-Peptide RBD 484–508 Induces IFN-γ T-Cell Response in Na-ïve-to-Infection and Unvaccinated Subjects with Close Contact with SARS-CoV-2-Positive Patients

Even though various anti-SARS-CoV-2 vaccines are available on the market, it is still unclear if these can promote long-lasting protection. Developing vaccines and pandemic control strategies require a thorough understanding of the adaptive immune response to SARS-CoV-2. IFN-γ is one of the key cytokines that lymphocytes release in response to viral in-fection, and it is essential for both innate and adaptive immunity. Murdoca M et al. report on 28 subjects who were unvaccinated and naïve to SARS-Cov-2 infection, and who had reported close and extended contact with COVID-19-positive patients. Based on the findings, T-cells infected with SARS-CoV-2 pseudovirus exhibit similar levels of

IFN-γ gene ex-pression and protein production when exposed to one of these peptides, RBD 484–508.57-62

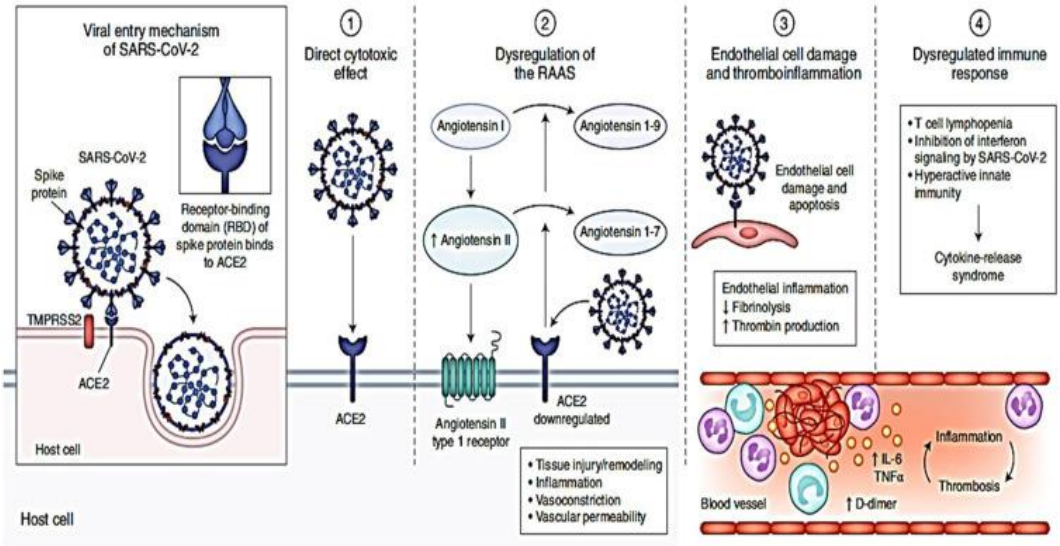

Figure 3. Pathophysiology of COVID-19 indicate virus entering the host cells through interaction of its spike protein with the entry receptor ACE2 in the presence of TMPRSS2.

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New COVID Variants and their Implications

Genetic variations of SARS-CoV-2 continue to be surfacing and spreading over the globe since the start of this outbreak. Towards the end of 2020, however, a number of new variants that were linked to a cata-strophic form of the condition and had enhanced transmission capability and infectiousness were found.3. These variations could be distinguished from other strains in circulation thanks to one or more mutations or spike protein substitutions. These variants were categorised into three types for convenience of understanding: variant of high consequence, variant of interest, and variant of concern (VOC) (Table 1).[75,76]. Depending on how a novel variant affects disease severity, diagnosis, treatment, vaccination, and transmission, it may or may not be included to one of these classifi-cations. As a result, based on the most recent scientific information, a variant's status may increase or decrease.

Variants of Interest (VOI)

WHO label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Impact on transmissibility	Impact on immunity	Impact on severity	Transmission in EU/EEA
Omicron	BA.2.75 (x)	India	(y)	May 2022	Unclear (1)	Similar to Baseline (2-4)	No evidence	Community
Omicron	XBB.1.5-like (a)	United States	N460K, S486P, F490S	n/a	Similar to Baseline (5, 6)	Reduced (v) (5, 7)	Similar to Baseline (8)	Community
Omicron	XBB.1.5-like + F456L (b) (e.g. **EG.5, FL.1.5.1, XBB.1.16.6**,	n/a	**F456L**, N460K, S486P, F490S	n/a	Baseline	Baseline (9)	Baseline	Dominant

	and **FE.1**)							
Omicron	BA.2.86	n/a	I332V, D339H, R403K, V445H, G446S, N450D, L452W, N481K, 483del, E484K, F486P	n/a	Unclear (10)	Unclear (10-12)	No evidence	Community

Variants under monitoring.

WHO label	**Lineage + additional mutations**	**Country first detected (community)**	**Spike mutations of interest**	**Year and month first detected**	**Impact on transmissibility**	**Impact on immunity**	**Impact on severity**	**Transmission in EU/EEA**
Omicron	XBB.1.16	n/a	E180V, T478R, F486P	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	DV.7.1	n/a	K444T, L452R, L455F	n/a	No evidence	No evidence	No evidence	Detected (a)
Omicron	XBB.1.5-like + L455F + F456L (b)	n/a	**L455F**, **F456L**, N460K, S486P, F490S	n/a	No evidence	No evidence	No evidence	Detected (a

Pathology and Postmortem Changes.

Lung	Severe squamous metaplasia with atypia, interstitial and intra-alveolar oedema, type 2 pneumocyte hyperplasia, capillary congestion, hyaline membranes, pneumocytic necrosis, and exudative and proliferative widespread alveolar damage
Liver	Pathological lesions, such as cardiac hypertrophy, atherosclerosis, general interstitial fibrosis, mild myocardial edoema, and atypical, minor, localised, and perivascular interstitial fibrosis, were seen in the livers of COVID-19-related deaths.
Brain	Microthrombi and acute infarcts, hypoxic alterations without any specific disease, and perivascular lymphocytic infiltration in the brainstem
Coagulation Abnormality	Disseminated intravascular coagulopathy (DIC), PE, deep vein thrombosis (DVT), arterial thrombosis, hypercoagulable coagulopathy, and intra-catheter thrombosis, among other thrombotic and/or thromboembolic complications.
Kidneys	Diffuse proximal tubule damage with brush boundary loss, non-isometric vacuolar degeneration, and frank necrosis were observed in the kidneys of COVID-19 patients.

Diagnosis

Microbiological testing is required for COVID-19 diagnosis. Individuals who experienced fever, respiratory symptoms, or a lower respiratory tract (LRT) infection are among those who should be tested. Those with a history of travel or those who have come into contact with suspected or confirmed COVID-19 cases are more likely to get the virus. The CDC and the Infectious Diseases Society of America (IDSA) had, however,

highlighted the patient priorities for COVID-19 testing, including symptomatic critically ill persons, front-liners, and individuals with risk indicators, because to limits in testing capacity. [90-97]

Table 1. Diagnostic approaches for COVID-19.

Types of diagnostic tests	Mechanism of detection	Source of samples	Result Interpretation
Nucleic acid amplification	Real Time PCR and NGS sequencing by using gene specific primer such as N,S,E and RdRP genes two independent sequences need to be detected	Nasal Swab, throat Swab, Bronchoalveolar lavage, blood faces and endotracheal aspirate	SARS-CoV2 Infection
Antibody based immunoassay	SARS-CoV2 IgM and IgG antibodies detection by ELISA	Serum	Immunity/Overall infection
Antigen based immunoassay	SARS-CoV2 detection protein	Nasal Swab, throat Swab, Bronchoalveolar lavage, blood faces and endotracheal aspirate	Confirm current SARS-CoV2
CT- Imaging	Clinical symptoms (Fever/Cough, epidemiological history imaging CT)	Radiological features	Trade to identify for further target

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)

CRISPR is an expedient method specifically designed to identify SARS-CoV-2. Early in 2020, the USA-FDA approved the technique as a substitute test for COVID-19 identification.The assay's sample pool is comparable to that of RT-PCR. SARS-CoV-2 DETECTR is an assay that uses loop-mediated amplification (LMA) to perform isothermal amplification and simultaneous recombinase polymerase amplification (RPA) from the extracted RNA, followed by Cas12 detection.[57-67] The SARS-CoV-2 DETECTR test has several advantages over RT-PCR for COVID-19 detec-tion. It requires fewer bulky apparatus, has an increased limit of detection, a quicker assay reaction time, and requires less assay sample. [68-87]

RECENT THERAPY IN MANAGEMENT OF COVID -19

High-Affinity Neutralizing DNA Aptamers against SARS-CoV-2 Spike Protein Variants

The ongoing emergence of novel SARS-CoV-2 variants that warrant concern has posed a challenge to current therapeutic approaches. In order to solve this, Ayass, M.A. et al. created a number of single-stranded DNA aptamers that both bind to the SARS-CoV-2 trimer S protein specifically and prevent it from interacting with ACE2 receptors. Short, single-stranded RNA or DNA molecules with a strong affinity for particular target mole-cules are known as aptamers. Since aptamers and their targets interact similarly to antigen-antibody interactions, they are frequently referred to as chemical antibodies. Aptamers, on the other hand, have a number of benefits over antibodies, including reduced size, decreased immunogen-icity, long stability and shelf life, less variation from batch to batch, ease of modification, affordability, and speed of production.

More versatility in the selection of aptamers for diverse targets, in-cluding peptides, proteins, small organic compounds, toxins, cells, vi-ruses, bacteria, etc., is made possible by the aptamers' flexible three-dimensional structures, which enable them to fold around

the in-tricate surfaces of their target molecules. A number of groups have recently discovered DNA aptamers that are capable of recognising the S protein of SARS-CoV-2. Most of them were devoted to creating aptamers that attach to the S protein's RBD or S1 domain.56-71

Inhibition of PERK Kinase, an Orchestrator of the Unfolded Protein Response (UPR), Significantly Reduces Apoptosis and Inflammation of Lung Epithelial Cells Triggered by SARS-CoV-2 ORF3a Protein

It was discovered that the SARS-CoV-2 ORF3a accessory protein was pro-apoptotic, involved in immunomodulation, and released the virus. To investigate a possible mechanism of ORF3a-induced apoptotic and in-flammatory death, ORF3a mRNA synthesised in vitro was transfected into lung epithelial cells (A549). It has been amply demonstrated that the protein plays a dynamic role as a "stress factor" for the endoplasmic re-ticulum, activating PERK kinase and other UPR-involved proteins and subsequently leading to the upregulation of their signalling pathway ex-ecuters (ATF6, XBP-1s, PERK, phospho eIF2a, ATF4, CHOP, GADD34). In light of the aforementioned, we note that PERK kinase is a "master tacti-cian" and that the emergence of ORF3a's apoptotic and inflammatory na-ture is primarily caused by its activation. As such, it may be a viable target for the development of novel therapeutic strategies.72-76

BREATHOX® Device Inhalation on Acute Symptoms Associated with COVID-19

According to Tanni, S. et al.'s hypothesis, patients with mild COVID-19 symptoms would have fewer respiratory symptoms when they used BREATHOX® to inhale NaCl particles. Thus, the main objective of this research was to compare the duration of COVID-19-induced acute symptoms to the standard of care (SOC) and assess the impact of oral and nasal inhalation of hypertonic NaCl particles (BREATHOX®). Secondly, we examined the incidence of unfavourable incidents associated with the use of the device.It was determined that BREATHOX® inhalation is safe and might help shorten the amount of time that COVID-19-induced coughing lasts.34-47

Role of Selective Digestive Decontamination in the Prevention of Ven-tilator-Associated Pneumonia in COVID-19 Patients

It has been reported that bacterial pneumonia, primarily ventila-tor-associated pneumonia (VAP), is a common complication in critically ill COVID-19 patients. The incidence of VAP ranges from 40 to 60%, and is approximately three times higher than in non-COVID-19 patients. assess whether the use of SDD in a systematic protocol for the prevention of ventilator-associated pneumonia (VAP) was successful in lowering the incidence of VAP in COVID-19 patients while maintaining the microbio-logical pattern of antibiotic resistance. Our pre-post observational study in COVID-19 patients, in light of other experiences, concludes that there is a correlation between the use of SDD in a structured protocol for VAP pre-vention and a decrease in the incidence of VAP, particularly late VAP, without an increase in the incidence of VAP caused by multidrug-resistant bacteria.67-78

Tocilizumab

A humanised monoclonal antibody directed against the IL-6 receptor is called tocilizumab. Early observational data indicated that tocilizumab treatment improved survival in hospitalised COVID-19 patients, espe-cially if the medication was given early in the course of the illness. These results are in opposition to the results of the early RCTs, which were un-derpowered to rule out a sizable therapeutic effect but were mainly neg-ative. Two sizable pragmatic RCTs afterwards showed an advantage in terms of mortality.[67-78]

Baricitinib

An oral inhibitor of Janus kinase 1 (JAK1) and JAK2 that has an-ti-inflammatory qualities is called baricitinib. A randomised controlled trial (RCT) involving 1,033 adult inpatients discovered that the combina-tion of baricitinib (4 mg/day, for up to 14 days) and the antiviral medication remdesivir reduced recovery time more effectively than remdesivir alone.

Table 2. SARS-CoV-2 candidate drug treatments in Phase III-IV trials.

Drug candidate	Description	Existing disease approval
Ritonavir	Anti-HIV Drug	Investigational combination
Lopinavir	Anti-viral	Investigational combination
Favipiravir	Antiviral agent against influenza	Influenza
Remdesivir	Viral RNA-dependent RNA polymerase	Broad spectrum anti-viral drug
Prezcobix	HIV-1 protease inhibitor	HIV infection
Galidesivir	Viral replication inhibitor	Antiviral against RNA viruses
Danoprevir	Inhibitors of NS3/4A	HCV Protease inhibitor
Umifenovir	Replication inhibitors	Anti-viral used for Influenza
Baloxavir marboxil (BXM)	Polymerase acidic endonuclease inhibitor	Anti-viral used for Influenza
Levovir	polymerase inhibitor	Anti-viral used for hepatitis B Virus
Dexamethasone	Anti-inflammatory	Rheumatoid arthritis
Oseltamivir	Neuraminidase inhibitor	Prevent Influenza A and B

Antiviral therapies

Antiviral drugs were not authorised for use in treating COVID-19 at the onset of the pandemic. As a result, a number of repurposed treatments that demonstrated antiviral effectiveness in vitro were examined in clinical trials before being used in clinical settings. More potent antivirals are now available, although many commonly used medications, including hy-droxychloroquine, lopinavir or ritonavir, and ivermectin, were demon-strated to be ineffective COVID-19 treatments when examined in well powered RCTs. [27,28, 26]

Remdesivir

Remdesivir is an analogue of a prodrug nucleoside that displays an-tiviral action against several RNA viruses in vitro, including SARS-CoV-2. Its active metabolite inhibits RNA-dependent RNA polymerase, reducing genome replication [29, 30]. Remdesivir has been investigated in both inpatient and outpatient COVID-19 patient situations.

Molnupiravir

An oral prodrug called molnupiravir is derived from β-D-N4-hydroxycytidine (NHC), an analogue of cytidine with broad-spectrum antiviral action against SARS-CoV-2 in vitro. As new RNA strands of the SARS-CoV-2 genome are synthesised, NHC is integrated into them, leading to a build-up of harmful mutations known as fatal muta-genesis. Molnupiravir decreased 29-day hospitalisation or mortality in the MOVe-OUT study, which included 1,433 adult outpatients with mild-to-moderate COVID-19. This was an impact that was not as signifi-cant as that seen with other antivirals. [99-105]

Antithrombotic therapies

Hospitalised COVID-19 patients had comparatively high rates of thrombotic and hemorrhagic sequelae, including venous thromboembo-lism (VTE), which can be fatal [48, 49]. Known as "COVID-19-associated coagulopathy," these problems arise from a state of malfunction in the thrombo-inflammatory coagulation system[50]. This coagulopathy's pathophysiology is unclear and appears to be complex. Acute-phase re-

actant coagulation factors (especially fibrinogen and factor VIII) at elevated levels can cause endothelial injury, which can be attributed to the virus or the anti-viral immune response. Other pro-inflammatory mechanisms, such as the creation of neutrophil extracellular traps, can also play a role [49,50,51, 52].

Neutralizing antibody therapies

Antibodies are essential for the adaptive immune response and for defending the body against infections. In order to neutralise a target virus by targeting it for elimination and preventing its entry into host cells, pathogen-specific polyclonal or monoclonal antibodies (mAbs) have been passively administered to control viral infections. This has led to the elimination of the infection-associated disease. Pathogen-specific neu-tralising antibodies can be produced as recombinant neutralising mAbs using proven molecular engineering techniques, or they can be trans-planted from patients who have recovered from a viral infection (known as convalescent plasma).[134-137]

Therapies targeting the RAAS

Therapies that inhibit the production of angiotensin II (ACE inhibi-tors), inhibit the binding of angiotensin II to the angiotensin type I receptor (ARBs), speed up the conversion of angiotensin II to angiotensin (recom-binant ACE2), or activate the angiotensin signalling (investigational drugs, including TRV–027 and TXA–127) are among those being assessed in randomised controlled trials. Recombinant ACE2 may also have the benefit of acting as a ruse for SARS-CoV-2, which could prevent viral spread.[132-133]

Development of SARS-CoV-2 Immunoglobulin based treatments option.

Leading candidate	**Description**
Convalescent plasma	Passively transfer antibodies (Immunoglobulin)
STI-5656 (Abivertinib)	Tyrosine kinase inhibitor
PRO 140 (Leronlimab)	Monoclonal antibody targeted against CCR5 receptor
PTC299	Dihydroorotate dehydrogenase inhibitors
CD24Fc	Immunomodulator (New drug)
Lenzilumab	Chronic Myelomonocytic leukemia
Tocilizumab	Immunosuppression
Sarilumab	Rheumatoid arthritis
Ravulizumab	Compliment inhibitors
Losmapimod	MAPK as potent suppressors of DUX4 expression
Pepcid H2 blocker	Mitigare (Colcrys) Anti-inflammatory agent

Therapies for acute respiratory failure

Although there are other possible ways that COVID-19 can induce severe disease, acute hypoxemic respiratory failure is still the main cul-prit. In treating COVID-19-induced respiratory failure, particular attention must be paid to the timing of intubation, the mode of oxygen delivery, the use of prone positioning, and the use of adjuvant therapies for refractory hypoxaemia, in addition to decisions about the use of antivirals, im-munomodulators, and anticoagulants, which may be beneficial to patients across the spectrum of illness.[130]

Oxygen delivery

For patients who need more oxygen than what a standard nasal can-nula can provide, there are three noninvasive methods available: high-flow nasal cannula (HFNC), which provides warmed and humidified oxygen through large-bore nasal cannulas at flow rates higher than the patient's peak inspiratory flow rate; or noninvasive ventilation (NIV), which uses a tight-fitting mask connected to a noninvasive ventilation machine to provide continuous positive airway pressure or bilevel posi-tive airway pressure.[131,132]

Prone positioning

Among those intubated for non-COVID-19 ARDS, prone positioning is one of the few therapies that has been demonstrated to lower mortality. Proning has not, however, been widely used in patients with COVID-19 ARDS due to persistent worries about its efficacy, resource usage, and potential to dislodge assist devices; data indicate significant inter-hospital variation in proning. Although proning in COVID-19 intubated patients has not been studied in randomised controlled trials, observational studies indicate that proning these patients early on may lower their mortality.

Adjunctive therapy for hypoxemia

The application of neuromuscular blockade in ARDS has been the subject of intense discussion in the years preceding the COVID-19 pan-demic. According to the 2019 Reevaluation of Systemic Early Neuro-muscular Blockade (ROSE) trial, neuromuscular blockade for 48 hours did not reduce 90-day mortality in patients with a partial pressure of arterial oxygen (PaO2) to fraction of inspired oxygen (FiO2) ratio less than 150 mmHg.

ECMO

ECMO may be a life-saving treatment for patients whose hypoxaemia is unresponsive to maximal ventilatory support, proning, neuromuscular inhibition, and inhaled pulmonary vasodilators. In patients with non-COVID-19 ARDS who had severe hypoxaemia, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial, which was reported in 2018, revealed a mortality advantage. During the COVID-19 pandemic, ECMO use surged significantly.

Vaccines

In the case of the COVID-19 pandemic, vaccinations are an essential and affordable means of preventing the illness and reducing its severity. A potent vaccine is essential for stopping the virus's transmission and re-ducing the severity of the illness. There are several vaccinations on the market right now, including subunit, mRNA, inactivated, and viral vector vaccines. According to preliminary statistics, adenoviral vector vaccina-tions were 73% along with messenger RNA (mRNA) vaccines were 85 percent successful among individuals who were 18 years of age or older. After receiving the first and second doses of the vaccine, people produce neutralising antibodies against the targeted area. Vaccine recipients can mount robust immune responses against SARS-CoV-2 RBDs using ade-novirus, mRNAs, and inactivated vaccines. [75-79]

Table 4. Tabular representation of ongoing clinical studies of vaccines for SARS-CoV-2.

Vaccine candidate	Details
mRNA-1273	mRNA-1273, a vaccine candidate based on previous study of SARS and MERS
Ad5-nCoV	Recombinant novel corona virus vaccine with adenovirus type 5 vector (Ad5)
ChAdOx1	SARS-CoV-2, adenovirus vaccine vector MERS vaccine.
INO-4800	DNA vaccine for SARS-CoV-2
BNT162	Modified mRNA-based, SARS-CoV-2 vaccine
NVX-CoV2373	Recombinant nanoparticle vaccine candidates for SARS-CoV-2
CureVac	mRNA-based SARS-CoV-2 vaccine
Vaxart	Oral recombinant SARS-CoV-2 vaccine; gene-based vaccine
DNA vaccine candidates	DNA-based vaccine for SARS-CoV-2
mRNA vaccine	Repurposed SARS vaccine and mRNA vaccine candidate
DNA plasmid vaccine candidate	Modified vaccinia ankara virus like particles (MVA-VLP) vaccine candidate for SARS-CoV-2
Adenovirus-based vector vaccine for SARS-CoV-2	Adenovirus-based vector vaccine for SARS-CoV-2
Modified avian coronavirus vaccine	Genetically similar avian coronavirus Infectious Bronchitis Virus
Gene-encoded antibody vaccine candidate	Next-generation, gene-encoded antibody vaccine for SARS-CoV-2
DPX- SARS-CoV-2	T-cell activating immunotherapy antigen vaccine

Intranasal DNA-based vaccine candidate	Stimulating an immune response in the nasal cavity
Single-dose patch delivery vaccine	Vaccine candidate for SARS-CoV-2 delivered through a single-dose patch

Nonetheless, these vaccines' effectiveness is assessed in the first six months following inoculation. Over time, the immune system progres-sively weakened, making breakthrough infections more frequent. Fur-thermore, SARS-CoV-2 mutations have the ability to undermine protection and infect vaccinated individuals. It is effective to reduce the severity and mortality of disease by increasing host immunity with extra vaccination doses, particularly in elderly patients. Given the young participants' low hospitalisation and fatality rates, as well as the possibility of a significant immune response to the initial doses of the vaccine, it is challenging to determine whether boosters have any positive effects. Nonetheless, indi-viduals with carcinomas and other immunosuppressive conditions have shown that current immunisations can elicit a sufficient immune response. Furthermore, variant-specific vaccinations have recently been created and licenced, but it is still unclear if they are exactly superior in real-world situations.[74-79]

Impact of new COVID 19 variants on vaccine

Variants of SARS-CoV-2, particularly VOCs, are a hazard to the on-going COVID-19 pandemic containment efforts. Certain variations may even have a higher capacity for transmission, different aetiology and ill-ness severity, and a connection to the sharp rise in COVID-19 cases and related hospitalisations. By changing the neutralising activity of mono-clonal and vaccine-elicited antibodies, the VOCs directly affect the COVID-19 vaccines and immunotherapeutics that are now on the market, causing a modest to significant loss of efficacy. As of right now, no SARS-CoV-2 variant has the capacity to become severe enough to be cat-egorised as a "variant of high consequence." It is impossible to completely rule out the prospect of such a variety emerging in the future, though. As a result, monitoring systems that can track the global appearance of new SARS-CoV-2 variants must be established. By putting prevention and control mechanisms in place early on, it will be possible to stop the spread of novel variations with significant consequences even if they do arise. [70-76]

FUTURE TRENDS

Intranasal gene therapy to prevent infection by SARS-CoV-2 variants

Since SARS-CoV-2 variants are more pathogenic and transmissible and can evade immunity, first-generation vaccines and monoclonal antibodies may no longer be as effective. A strategy to stop clinical consequences and the spread of SARS-CoV-2 variants was presented by Sims JJ et al. First, an angiotensin-converting enzyme 2 (ACE2) decoy protein was affinity ma-tured by Sims JJ et al., leading to 1000-fold improvements in binding across a variety of SARS-CoV-2 variants and distantly related ACE2-dependent coronaviruses. They then showed how this ruse could be expressed in the proximal airway when an AAV vector was administered intranasally. When administered intraperitoneally, this intervention successfully achieved therapeutic levels of decoy expression at the surface of proximal airways, thereby significantly reducing the clinical and pathologic con-sequences of the SARS-CoV-2 challenge in a mouse model.56-65

Single-dose skin patch-delivered SARS-CoV-2 spike vaccine

Although there are several vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the world still faces numerous obstacles in the implementation of these treatments. SARS-CoV-2 has sickened over 160 million people and killed over 3.3 million. A study uses the high-density microarray patch (HD-MAP) to apply a skin-based vac-cine against the spike subunit of SARS-CoV-2. They demonstrate how the vaccine is thermostable on the patches and how the administration of the patch boosts the immune system's cellular and antibody responses. Strong neutralisation of clinically significant isolates, such as the Alpha and Beta varieties, is achieved by evoked

antibodies. Finally, in an ACE2-transgenic mouse model, a single dose of HD-MAP-delivered spike offered total protection against a fatal virus challenge. Taken together, these findings demonstrate that HD-MAP administration of a SARS-CoV-2 vaccine out-performed conventional needle-and-syringe vaccination and could be a valuable contribution to the ongoing COVID-19 (coronavirus disease 2019) pandemic.66-71

Oral vaccination

An investigational COVID vaccination that can be given orally has been found to protect the host while also reducing the virus's airborne transmission to unprotected people. Still more research is required and being conducted.

Ethical considerations

The COVID-19 pandemic presents complex ethical challenges across diverse domains, encompassing resource allocation, physical distancing, public health surveillance, and healthcare workers' rights. These issues are compounded by variations in health systems, cultural contexts, and so-cioeconomic environments globally. Recognizing the imperative for eth-ical guidance, the World Health Organization (WHO) established the Working Group on Ethics and COVID-19. This international group offers guidance on ethical considerations in clinical care, research, and public health policymaking. Noteworthy activities include providing advice on COVID-19 study ethics, contributing to WHO guidelines, and formulating emergency protocols for human research committees. Additionally, WHO collaborates with the Access to COVID-19 Tools (ACT) Accelerator, ad-dressing diagnostics, therapeutics, and vaccine distribution ethically. The Global Health Ethics team at WHO coordinates international efforts, in-volving the Global Network of WHO Collaborating Centres for Bioethics and National Ethics Committees. The Public Health Emergency Prepar-edness and Response Ethics Network (PHEPREN) supports ethical deci-sion-making during global health emergencies, focusing on the COVID-19 pandemic.

Conclusion

Over the past four years, there has been a considerable improvement in our understanding of COVID-19 pathophysiology, clinical care, and therapies. The ongoing appearance of variations, however, seriously jeopardises the efficacy of treatment and prevention strategies. The failure to administer early antiviral agents, high rates of false-negative diagnoses, conflicting information regarding the effectiveness of specific therapeutic drugs, and the quick progression of these infections to severe conditions like ARDS, pulmonary embolism, disseminated intravascular coagulation, sepsis, and cytokine storm pose challenges to the clinical management of these infections. The international effort to combat COVID-19 is probably going to take a while until we find antiviral medications or vaccines that are 100% successful at preventing the disease from spreading. Further-more, as the pandemic fades, particular attention should be paid to the long-term effects like extended COVID-19, which could pose a significant healthcare problem in the years to come.

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