A REVIEW ON RECENT TRENDS IN CORONA VIRUS DISEASE PREVENTION AND TREATMENT METHODS AND RESEARCH DIRECTIONS FOR FUTURE

Chidurala Rahul[1], Dr.Heamavathi.S[2], K. Sushanth Sekhar[3], B.Geethika Reddy[4], Durga Prasad Thammisetty[5] , Renukaradhya Chitti[6], G.Venkata Nagaraju[7*]

[1] MBBS, Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu 600116, India.

[2] PG Scholar, Department of Pharmacology, Government Siddha Medical College, Arumbakkam, Chennai, India.

[3, 4] Department of Pharmacy Practice, SIMS College of Pharmacy, Mangaldas Nagar, Guntur, Andhra Pradesh, India.

[5]Associate Professor, Sri Padmavathi School of Pharmacy, Vyshnavi Nagar, Tiruchanoor Tirupati -517503.

[6] Research Scholar, Department of Pharmacy Practice, Adichunchanagiri College of Pharmacy Adichunchanagiri University, ACU Campus, NH75, B.G Nagara, Karnataka 571448.

[7] Assistant Professor, Department of Pharmacy Practice, SIMS College of Pharmacy, Mangaldas Nagar, Guntur, Andhra Pradesh, India.

***Corresponding Author**

G.Venkata Nagaraju

Assistant Professor Department of Pharmacy Practice SIMS College of Pharmacy Mangaldas Nagar, Guntur Andhra Pradesh, India

Email: drnagaraju.gv@gmail.com

Abstract

On March 11, 2020, the World Health Organization was forced to issue a pandemic declaration due to the outbreak's astonishing rate of geographic expansion. The seventh human-infecting coronavirus is the SARS-CoV-2, which also causes COVID-19. SARS caused about 10% of fatalities, whereas MERS caused up to 35%, making it one of the deadliest human viruses. It has been determined that the SARS-CoV-2 is substantially more transmissible from person to person. Containment of the disease is a difficult public health concern since it can spread swiftly and undetected through asymptomatic carriers and can be undetected for long periods of time. CRISPR technology, IgG assay, spike protein detection, and AI use are some current developments in diagnostic testing. The traditional reverse transcription polymerase chain reaction (RT-PCR) has also been enhanced with point-of-care quick assays. Supportive care,

mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) continue to be the standard of care, while other therapeutic options include mesenchymal stem cell therapy, convalescent plasma, monoclonal antibodies, hyperimmunoglobulin, RNAi, and antivirals, antiparasiticides, and anti-inflammatories. The many vaccine forms, including RNA, DNA, lentiviral, inactivated, and viral vector vaccines, are currently undergoing clinical studies. Ingenious vaccination delivery techniques are also being developed. The likelihood of a second wave of infection necessitates stringent and logical control methods in order to reduce fatalities to a minimum as governments have begun to let off on the lockdown measures. Lowering corona virus disease complications in the community may benefit from a better understanding of the improvements in diagnostic tools, therapies, vaccines, and stringent follow-up of COVID-19 control efforts.

Keywords: COVID-19, Pathogens, RT-PCR, ECMO, Antivirals, Vaccines, Clinical trials.

INTRODUCTION

Because changes in human behavior throughout the Neolithic period, roughly 12,000 years ago, have been attributed to viruses and viral infections, the social history of viruses has served as a general description of the impact of these agents on human history. The exponential increase in the spread of viruses that eventually became endemic was most prominent at this time, when humans started to expand their agricultural settlements. Viral pandemics have been caused by the rapid globalization and anthropogenic activities that have increased pathogenic transmission worldwide. The middle of the 19th century is notably remembered for harmful viral outbreaks and their multiplicity of relationships with both human and animal species. This further results in transmission between animals, posing a serious risk to human health and welfare. Around the beginning of the twenty-first century, it was discovered that a number of pandemics, particularly viral pandemics, had occurred as a result of the rapid globalization and human activity. The plague, cholera, and yellow fever pandemics, together with certain newly developing viruses including Ebola, Zika, SARS, Middle East Respiratory Syndrome (MERS), and COVID-19, have produced the most catastrophic pandemics in recorded human history. According to reports, over the past three decades, these viral pandemics have killed a sizable number of people and had a substantial impact on the global economy.

The COVID-19 epidemic, which started in Wuhan, Hubei Province, China, in December 2019, and quickly spread to the rest of the world in a short period of time, is currently the worst threat the world is currently facing. Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses that are a major cause of acute respiratory, hepatic, and neurological diseases with variable severity in vertebrates. They are best recognized by their pneumonia-like symptoms, which may also progress to major hypoxia and a number of cardiovascular complications (Wang et al., 2020). They are referred to as frequent human infections with a tendency for transient mutation and recombination. It results from the presence of spikes resembling crowns on the edges of these viruses, also known as coronaviruses. These coronaviruses are divided into four different families based on phylogenetic clustering, including alpha coronavirus (CoV), beta

coronavirus (CoV), gamma coronavirus (CoV), and delta coronavirus (CoV) (Huang et al., 2020). They include and CoVs, which are primarily found in bats and rodents and are known to infect people; however, and CoVs, which are primarily found in birds, are known to infect aves and mammals, including pigs (Paim et al., 2019). The CoVs (i.e., SARS-CoV and MERS-CoV) have been identified as having the highest fatality rates among all the classes of coronaviruses in addition to having the potential to infect a large percentage of people by bridging the inter-species barrier. They are structurally made up of four main proteins: (a) the spike protein (S), (b) the nucleocapsid protein (N), (c) the membrane protein (M), and (d) the envelope protein (E). Each of these proteins is essential for mediating the virus's attachment to the host receptor, its subsequent fusion, and for accelerating virus assembly within the host system.

Emergence and Evolution of SARS-CoV-2

Since the COVID-19 disease outbreak in December 2019 in Wuhan, China, epidemiologists have become more interested in analyzing the causes of the eruption of SARS-CoV-2 in humans, including the contribution of the animal reservoir, endemic circulation, co-infection, recombination events within RNA segments, and its time of species divergence. The open-air seafood market in Wuhan, China, was epidemiologically linked to instances of pneumonia in December 2019, prompting local Chinese officials to declare a complete lockdown and issue an epidemiological alert. After thorough investigation and clinical implications, researchers at Wuhan obtained a complete genome sequence from the infected individuals in January 2020 and discovered approximately 80% sequence similarity with SARS-CoV, establishing pneumonia as a SARS-induced disease (Zhou et al., 2020). This unique human pathogen was initially classified within the Sarbecovirus subgenus of the Coronaviridae family, which also includes SARS. From 2002 to 2003, the virus caused more than 8,200 infections. Subsequently, the virus did super-spread within China by mid-January 2020, and by mid-March 2020, it was given pandemic status. This in turn increased the medical community's desire to stop its spread, and at the same time, researchers worldwide were hard identifying the strain that was claiming millions of lives7-9.

Eventually, the results of the bioinformatics research showed that SARS-CoV-2 and other coronaviruses, particularly the betacoronavirus 2B, have genetic similarities. As a result, more research has been done on SARS-CoV-2 by treating it as a brand-new human-infecting member of the betacoronavirus 2B lineage (Boni et al., 2020). The full-length genome sequence of SARS-CoV-2 and the available genomes of beta coronaviruses were aligned, and researchers found that the genomes of SARS-CoV-2, SARS-like BatCov, and RaTG13 coronaviruses shared 96% of the same sequences. This suggests that SARS-CoV-2 originated from bats, or, in other words, that SARS-CoV-2 organically developed from bats.

SARS-CoV-2 Entry Portal in the Host Cell

Given that it comes into close contact with the outside environment, the respiratory tract is thought to be the main entry point for viruses into the mammalian body (Matrosovich et al., 2004). The respiratory system therefore hosts the predominant SARS-CoV-2 symptoms and consequences at this early stage. A COVID positive person releases the viral particles contained

in the droplets or aerosols when they are breathed by a healthy, uninfected person, and the SARS-CoV-2 binds to the particular cell-surface receptor for the viral protein. Eventually, the viral and lysosomal membranes fuse after it eventually enters the endosomes.

The host cells Transmembrane protease serine 2 (TMPRSS2) and lysosomal proteases (especially cathepsins) facilitate the entry of SARS-CoV and SARS-CoV-2 coronaviruses into the host through two distinct mechanisms: proteolytic cleavage of ACE2 receptor that stimulates viral uptake and cleavage of coronavirus spike glycoproteins that activates the glycoprotein for host cell entry.

Many studies have been done on these coronaviruses' host cell entry mechanisms, and they have revealed that both SARS-CoV and SARS-CoV-2 exhibit very identical mechanisms (Zou et al., 2020). The spike proteins attached to the virus surfaces act as a conduit for the virus entrance into the cell. A mature virus's spike protein is made up of a trimeric membrane-fusing S2 stalk and three receptor-binding S1 heads. The S1 subunit of spike protein with receptor-binding domain (RBD) first identifies the human angiotensin-converting enzyme-2 (hACE-2) as its receptor after the virus has been inhaled and entered the respiratory system by the healthy person (Zheng, 2020; Zou et al., 2020). In general, hACE-2 is a membrane-bound protein that is expressed in a wide variety of human cells, including those of the respiratory tract (particularly the lower respiratory tract), the vascular endothelium, the cardiovascular system, the kidneys, and the intestinal epithelium. Cell surface protease TMPRSS2 and lysosomal proteases (cathepsins) activity then causes the proteolytic activation of SARS spike protein at the S1/S2 barrier when hACE-2 is recognized by S1 (Wang et al., 2020). Due to their activity, S1 and S2 get separated, and the newly formed S2 molecule goes through significant conformational changes. This then causes the glycoprotein for host cell entry to be activated, leading to the ingression or release of viral RNA into the host cytoplasm, followed by the translation of new viral proteins and infecting neighboring cells.

A variation in the receptor (hACE-2) recognition and binding potential of RBD units in S1 glycoproteins on the surface of SARS-CoV and SARS-CoV-2 is claimed to affect the cellular entry mechanism for these viruses. It is well known that SARS-binding CoV-2's affinity for hACE-2 is considerably higher than that of SARS-CoV. Moreover, SARS-spike CoV-2's protein contains an additional proprotein convertase (PPC) domain, which separates it from SARS-CoV. (Berry et al., 2004; Wang et al., 2020).

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory syndrome coronavirus 2 infection that is extremely infectious (SARS-CoV-2). There have been more than 6 million deaths as a result of its terrible impact on the world. SARS-CoV-2 quickly spread throughout the world in a short period of time after the initial instances of this mostly respiratory viral infection were initially recorded in Wuhan, Hubei Province, China, in late December 2019. On March 11, 202010-18, the World Health Organization (WHO) was forced to declare it a global pandemic as a result of this.

While SARS-CoV-2 adapts to its new human hosts, it is susceptible to genetic evolution through the occurrence of mutations over time, giving rise to mutant variants that may differ from its

original strains in some ways. Many SARS-CoV-2 variations have been identified throughout this epidemic, but the WHO only lists a select subset of these as variants of concern (VOCs) because to their potential harm to public health around the world. Five SARS-CoV-2 VOCs have been discovered since the start of the pandemic, according to the WHO's epidemiological update:

- Alpha (B.1.1.7): the first concern variant described in the United Kingdom (UK) in late December 2020
- Beta (B.1.351) was initially discovered in South Africa in December 2020.
- Gamma(P.1): initially discovered in Brazil at the beginning of January 2021
- In India, Delta (B.1.617.2) was first discovered in December 2020.
- Omicron (B.1.1.529): Identified for the first time in November 2021 in South Africa

Etiology

Positive-stranded RNA(+ssRNA) viruses called coronaviruses (CoVs) have spike glycoproteins on their envelopes, which give them a crown-like appearance under an electron microscope (coronam is the Latin word for crown).

The subfamily Orthocoronavirinae of the Coronaviridae family classifies into four genera of CoVs:

- Alphacoronavirus (alphaCoV)
- Betacoronavirus (betaCoV)
- Deltacoronavirus (deltaCoV)
- Gammacoronavirus (gammaCoV)

The BetaCoV genus is further subdivided into five lineages or subgenera. According to genomic analysis, rodents and bats are likely the origins of alphaCoVs and betaCoVs. The gene sources of deltaCoVs and gammaCoVs, on the other hand, appear to come from bird species. CoVs are becoming the main cause of outbreaks of newly developing respiratory diseases. Animals of all kinds, including camels, cattle, cats, and bats, can develop respiratory, intestinal, hepatic, and neurological disorders from viruses belonging to this broad family. For unknown reasons, these viruses are able to infect people across species boundaries and can lead to illnesses ranging from the common cold to more serious conditions like MERS and SARS. There are now seven known human CoVs (HCoVs) that can infect people.

HCoV-OC43 and HCoV-HKU1 (betaCoVs of the A lineage); HCoV-229E and HCoV-NL63 are common human CoVs (alphaCoVs). In people with a functioning immune system, these viruses can cause upper respiratory tract infections and the common cold. Lower respiratory tract infections, however, can be brought on by these viruses in immunocompromised individuals and the elderly.

SARS and MERS are two additional human COVs (betaCoVs of the B and C lineage, respectively). These viruses are thought to be more virulent and are capable of igniting epidemics that appear as respiratory and extra-respiratory symptoms with a range of clinical severity.

The new HCoV's genome had 89% nucleotide identity with the bat SARS-like-CoVZXC21 and 82% with the human SARS-CoV, according to genomic analysis of a cluster-patient with atypical pneumonia who had visited Wuhan. The International Committee on Taxonomy of Viruses' scientists gave it the name SARS-CoV-2 as a result. The 9860 amino acids19–28 that make up the SARS-CoV-2 single-stranded RNA genome are encoded by 29891 nucleotides.

Despite the fact that SARS-origin CoV-2's is currently unknown, it is commonly believed to have come from an animal, supporting zoonotic transmission. SARS-CoV-2 likely evolved from a strain that was identified in bats, according to genomic analysis. There is a significant degree of homology (96%) between the human SARS-CoV-2 and the betaCoV RaTG13 of bats, according to the genomic comparison of the human SARS-CoV-2 sequence and known animal coronaviruses (Rhinolophus affinis).

SARS-CoV-2 Variants

SARS-CoV-2 is susceptible to genetic evolution, as was previously indicated, leading to a variety of variations that might differ from its ancestral strains in some ways. Particularly in the context of a worldwide pandemic, periodic genomic sequencing of viral samples is crucial since it aids in the discovery of any novel SARS-CoV-2 genetic variants. Importantly, there has been little genetic evolution since the establishment of the worldwide dominant D614G variation, which was linked to greater transmissibility but not the capacity to produce life-threatening illness.

In Denmark, an infected farmed mink is thought to be the source of another variety that was discovered in people; this variant did not have a higher transmissibility. Since then, numerous SARS-CoV-2 variants have been identified, of which a few are now known as variants of concern (VOCs) because of their potential to result in increased transmissibility or virulence, reduction in neutralization by antibodies acquired through natural infection or vaccination, ability to elude detection, or a reduction in the efficacy of therapeutics or vaccinations. As more variants of SARS-CoV-2 continue to emerge, the CDC and the WHO have independently developed a classification system to separate these variants into variants of concern (VOCs) and variants of interest (VOIs).

SARS-CoV-2 Variants of Concern (VOCs)

On the basis of whole-genome sequencing of samples from patients who tested positive for SARS-CoV-2, a new SARS-CoV-2 variant of concern, B.1.1.7 lineage, also known as Alpha variant or GRY (previously GR/501Y.V1), was discovered in the UK in late December 2020. The B.1.1.7 variation was found by genome sequencing as well as in a commonly used commercial test distinguished by the absence of the S gene (S-gene target failure, SGTF) PCR samples. The viral genome of the B.1.1.7 variant carries 17 mutations. Of these, the spike (S) protein has eight mutations (69-70 deletion, 144 deletion, N501Y, A570D, P681H, T716I, S982A, and D1118H). The spike protein's affinity for ACE 2 receptors is increased in N501Y, which facilitates viral attachment and subsequent penetration into host cells.

Beta (B.1.351 lineage)

Another SARS-CoV-2 form is B.1.351, often known as the Beta variant or GH501Y. The second wave of COVID-19 infections, caused by V2 with numerous spike mutations, was first discovered in South Africa in October 2020. Nine mutations (L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, and A701V) have been identified in the spike protein of the B.1.351 variation, three of which (K417N, E484K, and N501Y) are found in the RBD and increase the binding affinity for the ACE receptors29–31.

Gamma(P.1 lineage)

The P.1 version, sometimes referred to as the Gamma variant or GR/501Y.V3, is the third variant of concern. It was discovered in Brazil in December 2020 and was first discovered in the US in January 2021. Ten mutations in the spike protein are present in the B.1.1.28 variation (L18F, T20N, P26S, D138Y, R190S, H655Y, T1027I V1176, K417T, E484K, and N501Y). Similar to the B.1.351 variety, three mutations (L18F, K417N, and E484K) are present in the RBD. Importantly, this variation may be less neutralizable by post-vaccination sera, convalescent sera, and monoclonal antibody treatments.

Delta (B.1.617.2 lineage)

The fourth variety of concern, B.1.617.2, also known as the Delta variant, was discovered for the first time in India in December 2020 and was in charge of the deadly second wave of COVID-19 infections in India in April 2021. This variation was discovered for the first time in the US in March 2021. At first, the Delta variation was thought to be an interesting variant. Nonetheless, the WHO classified this type as a VOC in May 2021 as a result of its quick global spread.

Omicron (B.1.1.529 lineage)

Omicron was rapidly identified as a VOC as a result of more than 30 modifications to the virus' spike protein and the dramatic increase in cases seen in South Africa. The reported mutations include T91 in the envelope, P13L, E31del, R32del, S33del, R203K, G204R in the nucleocapsid protein, D3G, Q19E, A63T in the matrix, N211del/L212I, Y145del, Y144del, Y143del, G142D, T95I, V70del, H69del, A67V in the

Transmission of SARS-CoV-2

SARS-CoV-2 is mostly spread through respiratory droplet exposure from close contact or droplet transmission from presymptomatic, asymptomatic, or symptomatic persons who are carrying the virus. The airborne transmission of COVID-19 utilizing aerosol-generating techniques has also been linked to its spread. Nonetheless, evidence suggesting SARS-CoV-2 airborne transmission in the absence of aerosol-generating processes is surfacing and being assessed. This method of transmission hasn't, however, received widespread acceptance. Based on several investigations documenting the survivability of SARS-CoV-2 on different porous and nonporous surfaces, the fomite transmission from SARS-CoV-2 contamination of inanimate surfaces has been thoroughly defined. SARS-CoV-2 was found to be more stable on stainless steel and plastic surfaces than copper and cardboard ones during experimental testing, with the viable virus being found up to 72 hours after the surfaces were inoculated with the virus.

Viable virus was recovered from nonporous surfaces including glass and stainless steel for up to 28 days at 20 degrees C. In contrast, SARS-CoV-2 recovery on porous surfaces was lower than on nonporous surfaces. In a recent update, the Centers for Disease Control and Prevention (CDC) stated that although contact with SARS-CoV-2-contaminated surfaces can result in infection, the risk is low and this is not the predominant method of transmission. Patients with SARS-CoV-2 infection have the live virus present in their feces, according to epidemiologic data from many case investigations, indicating a potential for fecal-oral transmission.

Epidemiology

The World Health Organization (WHO) claims that the spread of viral illnesses poses a significant threat to the public's health. The severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak from 2002 to 2003, the H1N1 influenza pandemic in 2009, and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012 are just a few of the viral epidemics that have been blamed for the significant decline in global health over the past two decades. SARS-CoV-2, the virus that caused COVID-19, has spread to 223 countries since the WHO labeled it a worldwide pandemic, with more than 593 million illnesses and more than 6 million fatalities reported globally39.

Variations in COVID-19 based on age, gender, and the impact of medical comorbidities

People of all ages run the danger of getting this infection and serious illness. Those under the age of 60 and those with concomitant conditions (such as obesity, cardiovascular illness, chronic renal disease, diabetes, chronic lung disease, smoking, cancer, solid organ or hematopoietic stem cell transplant recipients) are more at risk of developing severe COVID-19 infection.

Pathogenesis of SARS-CoV-2

SARS-CoV-2 is composed of four main structural proteins: spike (S), envelope (E) glycoprotein, nucleocapsid (N), and membrane (M), as well as 16 nonstructural proteins and 5-8 auxiliary proteins. It is structurally and phylogenetically identical to SARS-CoV and MERS-CoV. The surface spike (S) glycoprotein, which has the appearance of a crown and is found on the outer surface of the virion, is cleaved into two subunits: an amino (N)-terminal S1 subunit that aids in the incorporation of the virus into the host cell; and a carboxyl (C)-terminal S2 subunit that mediates the fusion of the membranes of the virus and the host cell. The N-terminal domain (NTD), which enables viral entrance into the host cell and serves as a possible target for neutralization in response to antisera or vaccinations, and the receptor-binding domain (RBD) are further split into the S1 subunit. Since it serves as a binding site for the human ACE2 receptors, the RBD is a crucial peptide domain in the pathogenesis of infection. Inhibiting the renin-angiotensin-aldosterone system (RAAS), contrary to earlier theories, did not raise the risk of COVID-19 and other serious illnesses requiring hospitalization.

The SARS-CoV-2 spike or S protein (S1) binds to the many ACE2 receptors on respiratory epithelium, including type II alveolar epithelial cells, to allow SARS-CoV-2 access into the hosts' cells. In addition to the respiratory epithelium, the upper esophagus, enterocytes from the ileum, cardiac cells, proximal tubular cells of the kidney, and urothelial cells of the bladder all express ACE2 receptors. The host transmembrane serine protease 2 (TMPRSS2) primes the

spike protein S2 component after the viral attachment process, which enhances cell entrance and subsequent viral replication endocytosis with the formation of virions40.

The early and late phases of the pathophysiology of SARS-CoV-2 caused pneumonia provide the best explanation. An immune response is triggered by infected host cells in the late phase, which is characterized by the recruitment of T lymphocytes, monocytes, and neutrophils. These cells release cytokines like tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), interleukin-6 (IL-6), IL-1, IL-8, IL-12, and interfer When COVID-19 is severe, the immune system becomes too activated, generating a "cytokine storm" in which large quantities of cytokines, particularly IL-6 and TNF-, are released into the bloodstream and trigger both local and systemic inflammation. In patients with severe COVID-19, increased vascular permeability and the subsequent development of pulmonary edema are explained by a number of mechanisms, including: a) endotheliitis as a result of direct viral injury and perivascular inflammation, which leads to the deposition of microvascular and microthrombi; b) dysregulation of the RAAS due to increased binding of the virus to the ACE2 receptors; and c) activation of the kallikrein- Together with IL-6 and TNF-, SARS-CoV-2 attaching to the Toll-Like Receptor (TLR) causes the production of pro-IL-1, which is then broken down into the active mature IL-1 that causes lung inflammation up till fibrosis.

Effect of SARS-CoV-2 on Extrapulmonary Organ Systems

Although the respiratory system is the principal target for SARS-CoV-2 as described above, it can affect other major organ systems such as the gastrointestinal tract (GI), hepatobiliary, cardiovascular, renal, and central nervous system. SARS-CoV-2–induced organ dysfunction, in general, is possibly explained by either one or a combination of the proposed mechanisms such as direct viral toxicity, ischemic injury caused by vasculitis, thrombosis, or thrombo-inflammation, immune dysregulation, and renin-angiotensin-aldosterone system (RAAS) dys regulation.

Cardiovascular system (CVS): Although the exact mechanism of cardiac involvement in COVID-19 is unknown, it is likely multifactorial. ACE2 receptors are also exhibited by myocardial cells implicating direct cytotoxicity by the SARS-CoV-2 on the myocardium leading to myocarditis. Proinflammatory cytokines such as IL-6 can also lead to vascular inflammation, myocarditis, and cardiac arrhythmias.

Hematological: SARS-CoV-2 has a significant effect on the hematological and hemostatic systems. The mechanism of leukopenia, one of the most common laboratory abnormalities encountered in COVID-19, is unknown. Several hypotheses have been postulated that include ACE 2 mediated lymphocyte destruction by direct invasion by the virus, lymphocyte apoptosis due to proinflammatory cytokines, and possible invasion of the virus of the lymphatic organs. Thrombocytopenia is uncommon in COVID-19 and is likely due to multiple factors that include virus-mediated suppression of platelets, formation of autoantibodies, and activation of coagulation cascade that results in platelet consumption. Thrombocytopenia and neutrophilia are considered a hallmark of severe illness. Although it is well known that COVID-19 is associated with a state of hypercoagulability, the exact mechanisms that lead to the activation of the

coagulation system is unknown and likely attributed to the cytokine-induced inflammatory response. The pathogenesis of this associated hypercoagulability is multifactorial and is probably induced by direct viral-mediated damage or cytokine-induced injury of the vascular endothelium leading to the activation of platelets, monocytes, and macrophages, increased expression of tissue factor, von Willebrand factor, and Factor VIII that results in the generation of thrombin and formation of fibrin clot formation. Other mechanisms that have been proposed include possible mononuclear phagocytes induced prothrombotic sequelae, derangements in the renin-angiotensin system (RAS) pathways, complement-mediated microangiopathy.

Central Nervous System (CNS): There is emerging evidence of ACE2 receptors in human and mouse brains, implicating the potential infection of the brain by SARS-CoV-2. The possible routes by which SARS-CoV-2 can invade the central nervous system are transsynaptic transfer across infected neurons via the olfactory nerve, vascular endothelial cell infection, or migration of leukocytes across the blood-brain barrier.. Gastrointestinal (GI) Tract: The pathogenesis of GI manifestations of COVID-19 is unknown and is likely considered to be multifactorial due to several potential mechanisms that include the direct ACE 2-mediated viral cytotoxicity of the intestinal mucosa, cytokine-induced inflammation, gut dysbiosis, and vascular abnormalities.[64]

Hepatobiliary: Although the pathogenesis of liver injury in COVID-19 patients is unknown, hepatic injury in COVID-19 is likely multifactorial and is explained by many mechanisms alone or in combination that includes ACE-2-mediated viral replication in the liver, direct virus-mediated damage, hypoxic or ischemic injury, immune-mediated inflammatory response, drug-induced liver injury (DILI), or worsening of preexisting liver disease[41-45].

Renal: The pathogenesis of COVID-19 associated kidney injury is unknown and is likely multifactorial explained by a single or a combination of many factors such as direct cytotoxic injury from the virus, imbalance in the RAAS, associated cytokine-induced hyperinflammatory state, microvascular injury, and the prothrombotic state associated with COVID-19. Other factors such as associated hypovolemia, potential nephrotoxic agents, and nosocomial sepsis can also potentially contribute to kidney injury._ During the early phase of the pandemic, a seven-month study by Ziemba et.al reported that the deaths per 1,000 patients among ESRD patients during the pandemic exceeded the expected death rate among ESRD patients based on data from previous years prior to the start of the pandemic.

Clinical Manifestations of COVID-19

The median incubation period for SARS-CoV-2 is estimated to be 5.1 days, and the majority of patients will develop symptoms within 11.5 days of infection. The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical illness characterized by acute respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure. It is estimated that 17.9% to 33.3% of infected patients will remain asymptomatic. Conversely, the vast majority of symptomatic patients commonly present with fever, cough, and shortness of breath and less commonly with a sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias, and diarrhea.

Mild illness: Individuals who have any symptoms of COVID-19 such as fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, anosmia, or dysgeusia but without shortness of breath or abnormal chest imaging

Severe illness: Individuals who have (SpO2) ≤ 94% on room air; a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, (PaO2/FiO2) <300 with marked tachypnea with respiratory frequency >30 breaths/min or lung infiltrates >50%. Critical illness: Individuals who have acute respiratory failure, septic shock, and/or multiple organ dysfunction. Patients with severe COVID-19 illness may become critically ill with the development of acute respiratory distress syndrome (ARDS) which tends to occur approximately one week after the onset of symptoms.

Severe ARDS: PaO2/FiO2 ≤ 100 mmHg.

When PaO2 is not available, a ratio of SpO2/FiO2 ≤ 315 is suggestive of ARDS. A multicenter prospective observational study that analyzed 28-day mortality in mechanically ventilated patients with ARDS concluded that COVID-19 ARDS patients had similar ARDS features from other causes. The risk of 28-day mortality increased with ARDS severity.

Extrapulmonary Manifestations

Despite the fact that COVID-19, the disease brought on by SARS-CoV-2, mostly affects the respiratory system, given the various organ dysfunction it is connected with, COVID-19 might be regarded as a systemic viral infection. Renal manifestations: Acute kidney injury (AKI), which is frequently seen in patients hospitalized with severe COVID-19, is a risk for patients. AKI is likely multifactorial in the context of hypervolemia, drug injury, vascular injury, and drug-related injury, and may also be caused directly by the virus itself. The extrapulmonary symptom of COVID-19 that is most frequently observed is AKI, which is linked to a higher mortality risk. A significant multicenter cohort study of 5,449 COVID-19 patients admitted to the hospital found that of those, 1993 (36.6%) developed AKI during hospitalization, and of them, 14.3% required renal replacement therapy (RRT). Proteinuria, hematuria, electrolyte abnormalities such hyperkalemia and hyponatremia, and disturbances in the acid-base balance like metabolic acidosis are some other clinical and laboratory symptoms.

Evaluation

A detailed clinical history regarding the onset and duration of symptoms, travel history, exposure to people with COVID-19 infection, underlying preexisting medical conditions, and drug history should be elicited by treating providers. Patients with typical clinical signs suspicious of COVID-19 such as fever, cough, sore throat, loss of taste or smell, malaise, and myalgias should be promptly tested for SARS-CoV-2. Besides symptomatic patients, patients with atypical symptoms of COVID-19 or anyone with known high-risk exposure to SARS-CoV-2 should be tested for SARS-CoV-2 infection even in the absence of symptoms[46].

Diagnostic Testing In COVID-19

Molecular Testing

The standard diagnostic mode of testing is testing a nasopharyngeal swab for SARS-CoV-2 nucleic acid using a real-time PCR assay. Commercial PCR assays have been validated by the US Food and Drug Administration (FDA) with emergency use authorizations (EUAs) for the qualitative detection of nucleic acid from SARS-CoV-2 from specimens obtained from nasopharyngeal swabs as well as other sites such as oropharyngeal, anterior/mid-turbinate nasal swabs, nasopharyngeal aspirates, bronchoalveolar lavage (BAL) and saliva. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. SARS-CoV-2 antigen tests are less sensitive but have a faster turnaround time compared to molecular PCR testing.

Serology Testing

An antibody test can evaluate for the presence of antibodies that occurs as a result of infection. Antibody tests play an important role in broad-based surveillance of COVID-19, and many commercial manufactured antibody testing kits are available to evaluate the presence of antibodies against SARS-CoV-2 are available. Despite the numerous antibody tests designed to date, serologic testing has limitations in specificity and sensitivity, and results from different tests vary. However, an antibody test with a specificity higher than 99% and a sensitivity of 96% has been developed by the CDC, which can identify past SARS-CoV-2 infection.

Other Laboratory Assessment

Complete blood count (CBC), a comprehensive metabolic panel (CMP) that includes testing for renal and liver function, and a coagulation panel should be performed in all hospitalized patients. Additional tests such as testing for inflammatory markers such as ESR, C-reactive protein (CRP), ferritin, lactate dehydrogenase, D-dimer, and procalcitonin can be considered in hospitalized patients. However, their prognostic significance in COVID-19 is not clear[47].

Imaging Modalities

Considering this viral illness commonly manifests itself as pneumonia, radiological imaging has a fundamental role in the diagnostic process, management, and follow-up. Imaging studies may include chest x-ray, lung ultrasound, or chest computed tomography. There are no guidelines available regarding the timing and choice of pulmonary imaging studies in patients with COVID-19, and the type of imaging should be considered based on clinical evaluation.

Chest X-ray

Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes; it can be completely normal in the initial stages of the disease. In the more advanced stages of infection, the chest X-ray examination commonly shows bilateral multifocal alveolar opacities, which tend to confluence up to the complete opacity of the lung.

Chest Computed Tomography (CT)

Chest CT is not recommended for routine use as a primary imaging investigation or screening by the American College of Radiology. Chest computed tomography (CT), especially high-

resolution CT (HRCT), is the preferred diagnostic technique for assessing COVID-19 pneumonia, especially when the disease is coupled with progression.

Chest CT can reveal a number of general findings and radiologic abnormalities. The majority of these findings may also be seen in other lung infections caused by streptococcus, chlamydia, mycoplasma, influenza A (H1N1), CMV, SARS, and MERS. Multifocal bilateral "ground or ground glass" (GG) areas together with consolidation areas with patchy distribution, primarily peripheral/subpleural, and increased involvement of the posterior region's lower lobes are the most frequent CT findings in COVID-19. There is also evidence of the "crazy paving" pattern.

Lung Ultrasound

Ultrasonographic examination of the lung allows evaluating the progression of the disease, from a focal interstitial pattern up to a "white lung" with evidence of subpleural consolidations. Considering its noninvasive nature and zero risks of radiation, it is a useful diagnostic modality for patient follow-up and assists in determining the setting of mechanical ventilation and prone positioning.

The main sonographic features are:

Pleural lines: Appear often thickened, irregular, and discontinuous until it almost seems erratic; subpleural lesions can be seen as small patchy consolidations or nodules.

B lines: They are often motionless, coalescent, and cascade and can flow up to the square of white lung.

Thickenings: They are most evident in the posterior and bilateral fields, especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.

Perilesional pleural effusion

The early phase of the sickness can be distinguished by focal areas of fixed B lines, which is followed by a phase of numerical growth of the B lines up to the white lung and mild subpleural thickening. This progression continues until posterior consolidations48 are evident.

Treatment

Early in the pandemic, there was a lack of knowledge about COVID-19 and its therapeutic care, which made it urgent to use experimental therapeutics and drug repurposing to lessen the severity of this novel viral infection. Since then, tremendous advancements have been made as a consequence of the tireless efforts of clinical researchers around the world. These advancements have improved our understanding of COVID-19 and its management as well as sped up the discovery of novel medicines and vaccines.

Pharmacologic Therapies In The Management Of Adults With COVID-19

Antiviral medications (e.g., molnupiravir, paxlovid, remdesivir), monoclonal antibodies (e.g., bamlanivimab/etesevimab, casirivimab/imdevimab, sotrovimab, bebtelovimab), anti-inflammatory medications (e.g., dexamethasone), and immunomodulators (e.g.

Antiviral Therapies

Initially developed as a potential antiviral treatment for influenza, alphaviruses such as Eastern, Western, and Venezuelan equine encephalitic viruses, and named after the Norse god Thor's

hammer Mjölnir, molnupiravir is a directly acting broad-spectrum oral antiviral agent acting on the RdRp enzyme. A broad-spectrum antiviral drug called Remdesivir has previously shown antiviral effectiveness against SARS-CoV-2 in vitro. Initially during the pandemic, hydroxychloroquine and chloroquine were suggested as COVID-19 antiviral therapies. The clinical status or overall mortality of hospitalized patients treated with hydroxychloroquine with or without azithromycin did not improve when compared to placebo, according to data from randomized control studies.

During the early stages of the pandemic, lopinavir/ritonavir, an FDA-approved combination drug for the treatment of HIV, was suggested as an antiviral treatment for COVID-19.

Anti-SARS-CoV-2 Neutralizing Antibody Products

Uncertainty exists over the length of time that COVID-19 survivors' neutralizing antibodies against SARS-CoV-2 remain active. Nevertheless, substantial research is being done in ongoing clinical studies to determine their potential significance as therapeutic agents in the treatment of COVID-19.

Strong anti-spike neutralizing monoclonal antibodies, bamlanivimab and etesevimab (LY-CoV555 or LY3819253 and LY-CoV016 or LY3832479), are available. An anti-neutralizing monoclonal antibody called bamlanivimab was created from convalescent plasma from a COVID-19 patient. A neutralizing monoclonal antibody called bebtelovimab (LY-CoV1404, 1404) specifically targets the RBD of the spike(S) protein of the SARS-CoV-2 virus.

The FDA granted two separate EUAs in November 2020 and May 2021, approving REGN-COV2 (casirivimab and imdevimab) and sotrovimab for use in clinical trials. These EUAs restricted the use of these medications to nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection and mild to moderate COVID-19 who were at a high risk of developing severe disease and/or hospitalization.

Strong anti-spike neutralizing monoclonal antibodies, ixagevimab and cilgavimab (AZD7442), were produced from antibodies isolated from B cells of SARS-CoV-2-infected patients. These antibodies have shown neutralizing activity against the virus by binding to nonoverlapping epitopes of the viral spike-protein RBD.

Corticosteroids: The production of cytokines in severe COVID-19 is linked to inflammation-related lung injury that is defined by an increase in inflammatory markers.

IL-1 (interleukin) Antagonists: An interleukin-1 receptor antagonist called Anakinra has been given FDA approval to treat rheumatoid arthritis. Its off-label use in severe COVID-19 was evaluated in a small case-control study trial using the justification that the synthesis of cytokines, such as interleukin (I.L.)-1, is what causes severe COVID-19.**Janus kinase (JAK) inhibitors**

Patients with moderate to moderately active rheumatoid arthritis (RA) are currently prescribed baricitinib, an oral selective inhibitor of Janus kinase (JAK) 1 and JAK 2. Based on its inhibitory action on SARS-CoV-2 endocytosis in vitro and on the intracellular signaling pathway of cytokines that generate the late-onset hyperinflammatory state that culminates in severe disease, baricitinib was thought to be a possible treatment for COVID-19.

Another oral selective JAK 1 and 2 inhibitor, roxolitinib is prescribed for steroid-resistant GVHD, polycythemia vera, and myeloproliferative diseases. It has been proposed to have an inhibitory impact on the intracellular signaling pathway of cytokines, similar to baricitinib, making it a possible COVID-1949 therapy.

Another oral JAK 1 and JAK3 selective inhibitor, tofacitinib is prescribed for moderate to severe rheumatoid arthritis, psoriatic arthritis, and moderate to severe ulcerative colitis. It was assumed that its administration could lessen the viral inflammation-mediated lung harm in individuals with severe COVID-19 due to its inhibitory effect on the inflammatory cascade. Tofacitinib was associated with a lower risk of respiratory failure or death, according to the findings of a small randomized controlled trial that assessed the efficacy and included 289 patients who were randomly assigned to receive the drug or a placebo (PMID:34133856).

Acalabrutinib, ibrutinib, and rilzabrutinib are Bruton's tyrosine kinase inhibitors, which control macrophage signaling and activation and are currently FDA-approved for various hematologic malignancies. It is hypothesized that the immunological response characterized by hyperinflammation in severe COVID-19 results in macrophage activation.

Mild Illness

According to NIH recommendations, patients with minor illnesses can be managed in an outpatient setting with supportive care and isolation. Regularly, laboratory and radiographic tests are not necessary. Those who are elderly or who already have medical issues should be closely watched until they show signs of clinical improvement. Paxlovid or Remdesivir are the preferred medicines for outpatients who are at high risk of illness progression and have a low threshold for considering hospitalization for closer monitoring, according to the National Institutes of Health (NIH) Covid-19 treatment guidelines panel.

Moderate Illness

Patients with moderate COVID-19 illness should be hospitalized for close monitoring.

Remdesivir and dexamethasone can be considered for patients who are hospitalized and require supplemental oxygen.

Severe/Critical Illness

Hospitalization is necessary for patients with severe/critical COVID-19 sickness. Patients with severe COVID-19 are more likely to experience protracted critical illness and pass away, so it is important to talk about care objectives, go over advanced directives, and choose substitute medical decision-makers. Since that COVID-19 is linked to a prothrombotic condition, all patients should continue receiving prophylactic anticoagulation. When performing aerosol-generating procedures on patients with COVID-19 in the ICU, such as endotracheal intubation, bronchoscopy, tracheostomy, manual ventilation prior to intubation, physical pronation of the patient, or providing critical patient care like nebulization, upper airway suctioning, disconnecting the patient from the ventilator, and nonintubating procedures, clinicians and other healthcare staff must wear the proper PPE, which includes gowns, gloves.

Prevention of COVID-19

Vaccination to prevent SARS-CoV-2 infection

Those with old age and comorbid conditions such obesity, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic renal disease, chronic liver disease, and neoplastic disorders are at a higher risk for developing severe COVID-19 and its consequences. Acute respiratory failure, acute decompensation syndrome (ARDS), and/or multiorgan failure that leads in mortality are the most common side effects of a severe COVID-19 illness.

Patients with COVID-19 disease also have a higher risk of developing prothrombotic outcomes such as PE, DVT, MI, ischemic strokes, and arterial thrombosis. Cardiovascular system involvement results in cardiogenic shock, cardiomyopathy, and malignant arrhythmias.

Severe ileus, bowel ischemia, transaminitis, gastrointestinal bleeding, pancreatitis, Ogilvie syndrome, and mesenteric ischemia are among the common GI issues experienced by critically ill COVID-19 patients. A greater risk of death is associated with acute renal failure, the most prevalent extrapulmonary COVID-19 symptom.

Invasive secondary fungal infections including rhino-cerebro-orbital mucormycosis and pulmonary aspergillosis associated to COVID-19 are becoming more and more common in patients recovering from COVID-19. Uncontrolled diabetes, concurrent lymphopenia, and excessive corticosteroid use are comorbid conditions that increase the risk of secondary fungal infection.

Complications

Severe COVID-19 and its associated problems are more likely to occur in patients who are older and have concomitant illnesses such obesity, diabetes mellitus, chronic lung disease, cardiovascular disease, chronic kidney disease, chronic liver disease, and neoplastic disorders. The most frequent side effect of a severe COVID-19 sickness is clinical deterioration that develops gradually over time or all at once and causes acute respiratory failure, ARDS, and/or multiorgan failure that results in death.

Furthermore, prothrombotic events such PE, DVT, MI, ischemic strokes, and arterial thrombosis are more likely to occur in COVID-19 patients. Involvement of the cardiovascular system leads to cardiogenic shock, cardiomyopathy, and malignant arrhythmias.

In critically ill COVID-19 patients, GI problems include bowel ischemia, transaminitis, gastrointestinal hemorrhage, pancreatitis, Ogilvie syndrome, mesenteric ischemia, and severe ileus are frequently seen. The most frequent extrapulmonary symptom of COVID-19, acute renal failure, is linked to a higher mortality risk.

More and more cases of secondary invasive fungal infections in COVID-19 survivors have been documented, including pulmonary aspergillosis related with the virus and rhino-cerebro-orbital mucormycosis. Secondary fungal infections are susceptible to comorbid diseases such uncontrolled diabetes, concomitant lymphopenia, and excessive corticosteroid use.

Deterrence and Patient Education

The use of facemasks and travel precautions as per CDC recommendations, as well as social distancing state and local authorities' social distancing measures, must be promoted to patients

and their families. Patients must be instructed to regularly wash their hands for at least 20 seconds with soap and water after contact with contaminated surfaces. People should be informed about emergency care options and encouraged to use them when necessary. Patients should be informed about telehealth services and offered the choice to use them instead of office visits, if appropriate. High-risk patients should be urged to seek therapy as soon as possible and informed about cutting-edge therapeutic options such monoclonal antibodies.

Post-COVID-19 Complications

Acute disseminated encephalomyelitis, Guillain-Barre syndrome (GBS), acute necrotizing hemorrhagic encephalopathy (ANHE), acute neuropathy, etc., caused by a dysregulated immune response, cranial involvement, and a compromised central and peripheral nervous system are now seen as a post-COVID condition and have raised concerns. After a week of recuperating from COVID-19, individuals have also reported autoimmune disorders and multisystem inflammatory syndrome (MIS), a clinical disease in which edema develops in several body locations as a result of heightened proinflammatory cytokine production.

VACCINES

In order to distinguish between vaccines that contain the pathogen in its dead (inactivated, non-live) form and those that do not, vaccines can be classified as either live or non-live. Live vaccinations elicit a strong cellular and humoral response, whereas non-live vaccines primarily generate humoral immunity.

Inactivated virus vaccines

- CoronaVac
- WIBP-CorV
- BBIBP-CorV
- BBV152
- Protein subunit vaccines
- NVX-CoV2373
- FINLAY-FR-2
- Viral vector (non-replicating) vaccines
- ChAdOx1
- Ad26.COV2.S
- Gam-COVID-Vac
- Nucleic acid-based (RNA) vaccines
- BNT162b2
- mRNA-1273
- CVnCoV

Live attenuated virus vaccines

A weakened version of the virus is used in live attenuated viral vaccines, which are created such that they may successfully multiply in an immunological-competent host and elicit a strong

immune response. Live attenuated vaccines are less suited for use in this population because they may potentially reproduce in an uncontrolled way in immunosuppressed people.

vaccinations for inactivated viruses

In contrast, inactivated vaccinations either contain entire or altered pathogens that have been rendered inactive, preventing their multiplication. However, inactivated vaccines do not necessarily result in an immune response that is as potent or durable as a live attenuated vaccine.

Several viral proteins are presented by inactivated virus technology for immunological detection. They exhibit stable conformation-dependent antigenic epitope expression. Pitfalls include their capacity to change viral epitopes, which, if the native structure of the viral antigen is not preserved, may negatively affect immunogenicity.

Virus fragments are used in the construction of protein subunit vaccines. Protein subunit vaccines, like inactivated whole-cell vaccinations, do not include live pathogen components. These differ from inactivated whole-cell vaccines in that they only contain the pathogen's antigenic components required to elicit a protective immune response. The subunit vaccine is said to be a more dependable and secure method than inactivated vaccines because it only depends on the antigen of interest produced using recombinant technology.

Throughout the past few decades, a number of new platforms have emerged. They include viral vectors, virus-like particles, RNA and DNA vaccines based on nucleic acids, all of which have been used in the creation of the COVID-19 vaccine.**Viral vector vaccines**

Because they lack antigens, they are different from the majority of conventional vaccines. They are often built from a carrier virus, such as the adeno or poxvirus, and are designed to transmit the COVID19 vaccine's main target.

Nucleic acid-based vaccine – mRNA vaccine

Although mRNA vaccines are a relatively new vaccine type, scientists have been interested in this platform for many years. The way that mRNA vaccines work is by giving cells instructions on how to produce a protein that could result in an immune response. In order to avoid the risk of integration into the host genome, mRNA translation takes place in the cytoplasm of the host cell. Similar to viral vectors, mRNA vaccines trigger dendritic cell sensing. Since mRNA may activate TLR7, adjuvants are not necessary. These vaccines have the ability to elicit a CD8 T cell response, just like viral vectors, attenuated vaccinations, and DNA vaccines.

Nucleic acid-based vaccine – DNA vaccine

DNA vaccine candidates work by injecting an immune-stimulating plasmid with the DNA sequence encoding a SARS-CoV2 antigen. Plasmid DNA is biocompatible, produces inexpensively, and has a long shelf life, therefore DNA vaccine-based immunotherapeutic techniques have been created to treat infections. Nevertheless, mucosal SARS-CoV2 vaccines are currently being developed. These vaccinations are administered systemically (often by intramuscular injection). It is anticipated that this kind of vaccine will be more effective at preventing infection. Only one nasal vaccine, an attenuated influenza vaccine, has received approval thus far, COVID-19 being the exception. In December 2019, a brand-new -coronavirus

called SARS-CoV-2 surfaced in Wuhan (Hubei Province, China), where it was recognized as the cause of the COVID-19 outbreak.

CONCLUSION

As previously mentioned, SARS-CoV-2 primarily targets the respiratory system, but it can also have an impact on other significant organ systems, including the gastrointestinal tract (GI), hepatobiliary, cardiovascular, renal, and central nervous system. Generally speaking, the SARS-CoV-2-induced organ dysfunction may be explained by one or more of the proposed mechanisms, including direct viral toxicity, ischemic injury brought on by vasculitis, thrombosis, or thrombo-inflammation, immune dysregulation, and renin-angiotensin-aldosterone system (RAAS) dysregulation. Public education and enable better cooperation and outcomes of public health measures.

FUNDING

Not Applied for Funding

CONFLICT OF INTEREST

Authors are declared that no conflict of interest

ETHICAL CONSIDERATIONS

Not Applicable

ACKNOWLEDGEMENT

Not Applicable

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

INFORM CONSENT

Not Applicable

REFERENCES

1. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systematic review. *J. Med. Virol.* 92(5), 479–490 (2020).
2. Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat. Rev. Microbiol.* 11(12), 836–848 (2013).
3. Bhagavathula AS, Aldhaleei WA, Rovetta A, Rahmani J. Vaccines and drug therapeutics to lock down novel coronavirus disease 2019 (COVID-19): a systematic review of clinical trials. *Cureus* 12(5), e8342 (2020).
4. Bijlenga G. Proposal for vaccination against SARS coronavirus using avian infectious bronchitis virus strain H from The Netherlands. *J. Infect.* 51(3), 263 (2005).
5. Smith TR, Patel A, Ramos S et al. Immunogenicity of a DNA vaccine candidate for COVID-19. *Nat. Commun.* 11(1), 1–13 (2020).
6. Dhama K, Sharun K, Tiwari R et al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. *Hum. Vaccin. Immunother.* 16(6), 1232–1238 (2020).

7. 20. Wang F, Kream RM, Stefano GB. An evidence based perspective on mRNA-SARS-CoV-2 vaccine development. *Med. Sci. Monit.* 26, e924700–924701 (2020).
8. Triggle CR, Bansal D, Abd Farag EAB, Ding H, Sultan AA. COVID-19: learning from lessons to guide treatment and prevention interventions. *Msphere* 5(3), e00317-20 (2020).
9. Crisci CD, Ardusso LR, Mossuz A, Müller L. A precision medicine approach to SARS-CoV-2 pandemic management. *Curr. Treat. Options Allergy* 7, 422–440 (2020).
10. Mondal MRH, Bharati S, Podder P, Podder P. Data analytics for novel coronavirus disease. *Inform. Med. Unlocked* 20, 100374 (2020).
11. Mulligan MJ, Lyke KE, Kitchin N et al. Phase I/II study of COVID-19 RNA vaccine BNT162b1 in adults. *Nature* 586(7830), 589–593 (2020).
12. Tai W, He L, Zhang X et al. Characterization of the receptor-binding domain (RBD) of 2019 novel coronavirus: implication for development of RBD protein as a viral attachment inhibitor and vaccine. *Cell. Mol. Immunol.* 17(6), 613–620 (2020).
13. Zhang N, Li C, Hu Y et al. Current development of COVID-19 diagnostics, vaccines and therapeutics. *Microbes Infect.* 22(6-7), 231–235 (2020).
14. Chang F-Y, Chen H-C, Chen P-J et al. Immunologic aspects of characteristics, diagnosis, and treatment of coronavirus disease 2019 (COVID-19). *J. Biomed. Sci.* 27, 1–13 (2020).
15. Kalita P, Padhi A, Zhang KY, Tripathi T. Design of a peptide-based subunit vaccine against novel coronavirus SARS-CoV-2. *Microb. Pathog.* 145, 104236 2020).
16. Baruah V, Bose S. Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV. *J. Med. Virol.* 92(5), 495–500 (2020).
17. Shi J, Zhang J, Li S et al. Epitope-based vaccine target screening against highly pathogenic MERS-CoV: an in silico approach applied to emerging infectious diseases. *PLoS ONE* 10(12), e0144475 (2015).
18. Xie Q, He X, Yang F et al. Analysis of the genome sequence and prediction of B-cell epitopes of the envelope protein of Middle East respiratory syndrome-coronavirus. *IEEE/ACM Trans. Comput. Biol. Bioinform.* 15(4), 1344–1350 (2017).
19. Syomin B, Ilyin Y. Virus-like particles as an instrument of vaccine production. *Mol. Biol.* 53(3), 323–334 (2019).
20. Du L, Yang Y, Zhou Y, Lu L, Li F, Jiang S. MERS-CoV spike protein: a key target for antivirals. *Exp. Opin. Ther. Targets* 21(2), 131–143 (2017).
21. Wang Q, Wong G, Lu G, Yan J, Gao GF. MERS-CoV spike protein: targets for vaccines and therapeutics. *Antiviral Res.* 133, 165–177 (2016).
22. Du L, Tai W, Yang Y et al. Introduction of neutralizing immunogenicity index to the rational design of MERS coronavirus subunit vaccines. *Nat. Commun.* 7(1), 1–9 (2016).
23. Wu C-Y, Monie A, Pang X, Hung C-F, Wu T. Improving therapeutic HPV peptide-based vaccine potency by enhancing CD4+ T help and dendritic cell activation. *J. Biomed. Sci.* 17(1), 1–10 (2010).
24. Lythgoe MP, Middleton P. Ongoing clinical trials for the management of the COVID-19 pandemic. *Trends Pharmacol. Sci.* 41(6), 363–382 (2020).

25. Zhang S, Huang W, Zhou X, Zhao Q, Wang Q, Jia B. Seroprevalence of neutralizing antibodies to human adenoviruses type-5 and type-26 and chimpanzee adenovirus type-68 in healthy Chinese adults. *J. Med. Virol.* 85(6), 1077–1084 (2013).
26. Li E, Yan F, Huang P et al. Characterization of the immune response of MERS-CoV vaccine candidates derived from two different vectors in mice. *Viruses* 12(1), 125 (2020).
27. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac. J. Allergy Immunol.* 38(1), 1–9 (2020).
28. Wang H, Zhang Y, Huang B et al. Development of an inactivated vaccine candidate, BBIBP-CorV, with potent protection against SARS-CoV-2. *Cell* 182(3), 713–721 e719 (2020).
29. Merante D. SARS-CoV-2, from its current highly contagious spreading toward the global development of an effective and safe vaccine: challenges and uncertainties. *Expert Opin. Drug Saf.* 19(7), 771–774 (2020).
30. Locht C. Vaccines against COVID-19. *Anaesth. Crit. Care Pain Med.* 39(6), 703–705 (2020).
31. Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to Phase 3 vaccine candidates. *Lancet* 396(10262), 1595–1606 (2020).
32. Kaur SP, Gupta V. COVID-19 vaccine: a comprehensive status report. *Virus Res.* 288, 198114 (2020).
33. Baden LR, El Sahly HM, Essink B et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* 384, 403–416 (2020).
34. Polack FP, Thomas SJ, Kitchin N et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. *N. Engl. J. Med.* 383(27), 2603–2615 (2020).
35. Xu J, Zhao S, Teng T et al. Systematic comparison of two animal-to-human transmitted human coronaviruses: SARS-CoV-2 and SARS-CoV. *Viruses* 12(2), 244 (2020).
36. Jha AK, Kumar R, Goenka MK, Dayal VM. Emerging treatment and prevention strategies against COVID-19: a brief update. *J. Dig. Endosc.* 11(1), 69 (2020).
37. Abboud H, Zheng C, Kar I, Chen CK, Sau C, Serra A. Current and emerging therapeutics for neuromyelitis optica spectrum disorder: relevance to the COVID-19 pandemic. *Mult.Scler.Relat.Disord.* 44, 102249 (2020).
38. Colloca S, Barnes E, Folgori A et al. Vaccine vectors derived from a large collection of simian adenoviruses induce potent cellular immunity across multiple species. *Sci. Transl. Med.* 4(115), 115ra112–115ra112 (2012).
39. ECDC, Infection Prevention and Control for COVID-19 in Healthcare Settings-First Update 12 March 2020, ECDC, Solna Municipality, Sweden, 2020.
40. J. Gawn, M. Clayton, C. Makison, B. Crook, and H. Hill, "Evaluating the protection afforded by surgical masks against influenza bioaerosols," Health and Safety Executive, vol. 36, pp. 276–282, 2008.

41. G. Musinguzi and B. O. Asamoah, ",e science of social distancing and total lock down: does it work? Whom does it benefit?" Electronic Journal of General Medicine, vol. 17, no. 6, pp. 17–19, 2020.
42. C. Sheridan, "Convalescent serum lines up as first-choice treatment for coronavirus," *Nature* Biotechnology, vol. 38, no. 6, pp. 655–658, 2020.
43. K. Duan, B. Liu, C. Li et al., "Effectiveness of convalescent plasma therapy in severe COVID-19 patients," Proceedings of the National Academy of Sciences of the United States of America, vol. 117, no. 17, Article ID 202004168, 2020.
44. European Commision, An EU Programme of COVID-19 Convalescent Plasma Collection and Transfusion Guidance onCollection, Testing, Processing, Storage, Distribution andMonitored Use, European Commision, Brussels, Belgium, 2020.
45. X. Tian, C. Li, A. Huang et al., "Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody," Emerging Microbes & Infections, vol. 9, no. 1, pp. 382–385, 2020.
46. M. Wang, R. Cao, L. Zhang et al., "Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro," Cell Research, vol. 30, no. 3, pp. 269–271, 2020.
47. A. Sch¨ogler, B. S. Kopf, M. R. Edwards et al., "Novel antiviral properties of azithromycin in cystic fibrosis airway epithelial cells," European Respiratory Journal, vol. 45, no. 2, pp. 428–439, 2015.
48. C. S. Benvindo, M. ,aler, A. Tas et al., "Suramin inhibits SARS-CoV-2 infection in cell culture by interfering with early steps of the replication cycle," BioRxiv, p. 2020, 2020.
49. L. Caly, J. D. Druce, M. G. Catton, D. A. Jans, and K. M. Wagstaff, ",e FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro," Antiviral Research, vol. 178, Article ID 104787, 2020.
50. M. Bray, C. Rayner, F. No¨el, D. Jans, and K. Wagstaff, "Ivermectin and COVID-19: a report in antiviral research, widespread interest, an FDA warning, two letters to the editor and the authors' responses," Antiviral Research, vol. 178, Article ID 104805, 2020.
51. L. E. Hensley, E. A. Fritz, P. B. Jahrling, C. Karp, J. W. Huggins, and T. W. Geisbert, "Interferon-β 1a and SARS coronavirus replication," Emerging Infectious Diseases, vol. 10, no. 2, pp. 317–319, 2004.