International Journal of Biomedicine 10(4) (2020) 303-311
http://dx.doi.org/10.21103/Article10(4)_GE

COVID-19 Infection

Guest Editorial

INTERNATIONAL JOURNAL OF BIOMEDICINE

SARS-CoV-2 Biochemistry, Transmission, Clinical Manifestations, and Prevention

Gundu H. R. Rao, Emeritus Professor

Laboratory Medicine and Pathology
Director of Thrombosis Research, Lillehei Heart Institute
University of Minnesota, Minneapolis, USA

Abstract

The first human case of COVID-19, caused by the novel coronavirus, was reported by health officials in the city of Wuhan, China, in December of 2019. The virus was identified as a novel coronavirus in early January 2020, and its genetic sequence was shared publicly on January 11, 2020. The novel virus, previously called 2019-novel coronavirus (2019-nCoV), is currently designated as the severe respiratory syndrome coronavirus-2 (SARS-CoV-2). On January 23, Wuhan was locked down, and the World Health Organization (WHO) declared a "public health emergency of international concern." The viral genome of SARS-CoV-2 is around 29.8 kilobase, containing six major open reading frames. The most common clinical symptoms were fever, cough, fatigue, shortness of breath, dyspnea, muscle ache, headache, chest pain, vomiting, sore throat, and sputum production. The main mode of transmission is through respiratory particles. The incubation period is 3 to 7 days. Both asymptomatic and symptomatic patients seem to be infectious. Spike (S) proteins of SARS-CoV-2 seem to have a 10- to 20-fold higher affinity to the human angiotensin enzyme 2 (ACE2) receptor than that of SARS-CoV. The high affinity of S protein to theACE2 receptor, and the additional advantages offered by the transfection facilitators Furin and Neutropilin-1, likely, contributes to the rapid spreading of this novel virus. Since these receptors are highly expressed on a variety of cells, including vascular endothelial cells and adipose tissue, individuals with compromised function of these tissues drive greater infection and severity in patients with COVID-19. Global health experts estimate that one in five individuals worldwide could be at risk for severe COVID-19, due to underlying health conditions. There is a great need for a rapid, specific, cost-effective test for monitoring the infected individuals. Even though a 15- minute, antigen test was made available by Abbott recently, it seems that the schools, colleges, and business establishments lack the ability to use these tests effectively to keep their businesses open safely. Management of the infected individuals seems to be based on clinical symptoms that manifest as the disease progresses. The US Food & Drug Administration (FDA), has created a special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program (CTAP). The program uses every available method to move new and emerging treatments as quickly as possible, keeping in mind the safety and efficacy of such therapies. According to the WHO report, there are currently more than 150 COVID-19 vaccine candidates under development. Several vaccines are in Phase 3 clinical trials. In an unprecedented effort, one of the experimental monoclonal antibody cocktails of Regeneron was used for therapeutic purposes when the US president was tested positive for COVID-19. There are no drugs or other therapeutics approved by the US FDA to prevent or treat COVID-19. The National Institutes of Health (NIH) have published interim guidelines for the medical management of COVID-19. In the absence of a cure, the only choice we all have is to follow the best practices recommended by the public health experts—use of face masks (coverings), frequent hand washing with soap, contact tracing of infected individuals, and quarantining COVID-19 positive individuals, till they are free of the highly infectious virus. (**International Journal of Biomedicine. 2020;10(4):303-311.**)

Key Words: COVID-19 • clinical trial • vaccine • public health

Introduction

SARS-CoV-2, the most potent killer virus, has caused an unprecedented pandemic worldwide. It has rapidly spread, and as of today (November 2, 2020), the virus has infected more than 44 million individuals and caused 1.2 million deaths. The USA (9.24 M), India (8.29 M), and Brazil (5.5 M) are the top three countries, with the highest number of COVID-19 positive cases (coronavirus.jhu.edu/map.html). Science magazine (ScienceMag.org) has been publishing titles of current articles, which serve as a great source of information on the Latest Coronavirus Research.

A recent Comment (September 26, 2020), published in the journal Lancet, says that COVID-19 is not a pandemic—it is a syndemic. Syndemics involve the clustering of two or more diseases within a population; the biological, social, and psychological interaction of those diseases; and the large-scale social forces that precipitate disease clustering in the first place.[1] According to the experts, a syndemic approach reveals biological and social interactions, that are important for prognosis, treatment, and health policy. Therefore, limiting the harm caused by SARS-CoV-2 will demand far greater attention, to Noncommunicable Diseases (NCDs), and socioeconomic inequality, than has hitherto admitted. Disparities that exist in the rate of infection and severity of this disease in the African American and minority communities, substantiate this observation by the experts. For just argument sake, COVID-19, for instance, is a pandemic over another pandemic— cardiometabolic disease. If we were to stretch our imagination further, we will have to include all the metabolic disease risk factors also as co-existing conditions. Addressing COVID-19 management, therefore, means, addressing all the metabolic risk factors as well as metabolic diseases such as; hypertension, excess weight, endothelial dysfunction, inflammation, obesity, diabetes, vascular diseases, and chronic respiratory diseases. SARS-CoV-2 pandemic is a public health workers nightmare, as well as that of critical care workers.[2-8]

The "Spanish" influenza pandemic of 1918-1919—the mother of all the pandemics, which infected more than a quarter of the global population at that time, and caused 50 million deaths worldwide, came in several successive waves. [9] According to the researchers of Armed Forces Institute of Pathology, Bethesda, Maryland, 75 years of research failed to answer the most basic question about the 1918 pandemic: why was it so fatal? Did some critical viral genetic event produce a 1918 virus of remarkable pathogenicity? After over a century, we have been confronted with the same question again, about the pathogenicity and the severity of SARS-CoV-2, which has devastated the global health and economies. The first pandemic influenza wave appeared in the spring of 1918, followed in rapid succession by much more fatal second and third waves, in the fall and winter of 1918-19, respectively. Dr. Michael Osterholm, the director for the Center of Infectious Disease Research and Policy at the University of Minnesota, now says, -the wave model doesn't seem to apply to this disease, "I don't see we're going to see one, two and three waves – I think we're just going to see one very difficult forest of fire cases." The epidemic is now entering a more serious and complex period. In just three days, globally, over one million COVID-19 positive cases were reported. In the US, currently, we are seeing more than 90,000 COVID-19 test positive cases per day and it is predicted to exceed 100,000 a day soon. The estimated cost of the COVID-19 pandemic is more than $16 trillion, or approximately 90% of the gross domestic product of the US.[10]

Evidently, the great unmet need of the day worldwide—is the availability of a safe, rapid, specific, and inexpensive test for population screening for the virus. During a pandemic, the first thing that the public health workers need is the ability to track and manage the spread of the pathogen. Since SARS-CoV-2 was a novel virus, new tests had to be developed for testing. China developed its own test. The WHO adapted a test that was developed in Germany. The WHO supplied tests for over 150 countries. The Center for Disease Control (CDC), decided to develop its own test, as is the usual case in the USA. Jeremy Konyndyk, a senior policy fellow at the Center for Global Development explained, "That's how we normally do things. A lot of countries don't have the capabilities that we have here. And therefore, the need to rely on WHO, to provide tests to them. We don't have to do that in the United States." According to The New York Times, Health and Human Services (HHS) Secretary, Mr. Alex Azar was 'unable' to get either CDC or the FDA to 'speed up or change course.' "Moreover, he had been at odds for months with the 'White House' over other related issues." Experts put the failure simply: "The reason for the lack of sufficient testing has been such a damaging shortcoming in the U.S. response, it has basically left us blind to the spread of the virus in our country for six or seven weeks." Without enough testing, the response will continue to fall short. Now the public health workers as well as the White House Coronavirus Task Force have given up the idea of contact tracing entirely.

Because of the many types of tests available worldwide, there is considerable confusion regarding the sensitivity and efficacy of these tests. None of the tests detect the live virus, which must be confirmed only by culturing the virus. There are currently two types of tests: molecular and antigen testing. Molecular tests include; PCR test, viral RNA test, and nucleic acid tests. These tests look for genetic material that comes only from the virus. A molecular test using a deep nasal swab is usually the best option because it will have fewer false negative results. The other test is the antigen test, which detects protein fragments (antigens) from the virus. The reported rate of false negative results is a high as 50%, which is why the antigen tests are not favored by the FDA, as a single test for monitoring active infection. Abbott's rapid point-of-care test achieved a sensitivity of 93.3% and specificity of 98.4% in 1,003 subjects in a post-authorization study. Abbott's fast, 15-minute, easy-to-use COVID-19 antigen test, and received FDA emergency use authorization. The mobile App provided by Abbott displays test results, to help develop protocols for a safe return of individuals to working places, such as schools, colleges, and various business establishments. However, the reality is far from the claims made by the manufacturers and promoters. Despite the availability of these tests, schools, colleges, and businesses have not been able to accomplish testing, tracking of positive cases, and managing the overall spread of the infections. Therefore, the efforts of schools, colleges, restaurants, and various other business centers have failed, to achieve the goals of a safe opening of the working places. Brandsma and associates have reported a new, rapid, sensitive, and specific assay using CRISPR technology, which seems to be superior to the qRT-PCR method.[11]

To add to the confusion of the testing fiasco, in a recent article in JAMA (October 8, 2020), Andy Slavitt a Distinguished Fellow at the Leonard Davis Institute of Health Economics, University of Pennsylvania, reflects on the global pandemic and questions about what kind of science, the

society is not effectively using.[12] He goes further to say, "that the greatest unmet need in successfully fighting coronavirus disease 2019 in the US relates, to the insights provided by the social sciences, rather than by the traditional biomedical sciences. Sociologists and Psychologists are as important in this crisis as virologists and epidemiologists." We partially agree with the fact that in an unprecedented health crisis, sociologists and psychologists are needed to help the affected individuals and their families. Having said that, we would like to inform the readers, of the great contributions of biomedical scientists, cellular and molecular biologists, biotechnologists, epidemiologists, emergency medicine staff, clinicians, and critical care workers. The fact that a reputed journal like the Journal of American Medical Association published this article, indicates the confusion that exists in COVID-literature. No one is disputing the role of other associated sciences in the management of the COVID-19 pandemic and its impact on the global population. But the role of traditional biomedical sciences cannot be ignored.

Next to rodents, bats form the second largest mammalian species in existence and are found just about everywhere. A 2017 study of 12, 333 bats, found that almost 9% carried at least one of 91 distinct coronaviruses, and there are at least 3200 coronaviruses that infect bats. They are the natural hosts, for a whole host of known viruses such as Rabies, Ebola, SARS-CoV, HKU1, and OC43, which cause the common cold.[12] Jay Cohen reported as early as in January of 2020, in Science journal, that Chinese researchers have characterized a draft genome of the virus implicated in the Wuhan outbreak. [14] According to the Center for Infectious Disease Research and Policy (CIDRAP Jan 11, 2020), in quickly moving developments, health officials from Wuhan, China, posted a novel outbreak of coronavirus, as well as released the genetic sequence of the 2019-nCoV.[15] Based on this information, the same day, the WHO released several interim guidance documents, including travel advice, the need for lab testing, and medical evaluation. Researchers from the IBM Watson Research Center, New York, published details of their findings on variant analysis of SARS-CoV-2 in May of 2020 in the WHO Bulletin.[16] The virus showed a high nucleotide sequence homology, with two severe acute respiratory syndrome viruses—SL-CoVZC45 (88%) and with SARS-CoV (80%). SARS-CoV-2 is a coronavirus with a 29, 903-base pair (bp), single-stranded RNA genome, containing 14 open reading frames and 27 estimated proteins. The Consortium of Global Initiative on Sharing All Influenza Data (GISAID) classifies this virus into 2 main clades based on their origin: (1) clade 19A originating from China, and (2) clade 20A originating from Europe. Phylogenic analyses of the Los Angeles isolate, with genomes from New York, Washington-State, and China, found that they shared similarities to all subclades, derived from these regional locations.

According to the early reports, the virus causes the coronavirus disease 2019 (COVID-19), with common symptoms such as fever, cough, shortness of breath, and fatigue. Early data indicated, that about 20% of patients who developed severe COVID-19, required hospitalization, including 5% who needed intensive care. Initial estimates of the case fatality rate (CFR) were from 3.4% to 6.6%. The older the patients, the more severe the illness. In the early reports from China, the median age of patients was 51 years. They did not report any significant difference in age distribution between male and female patients. The overall CFR was 5.6%, which was significantly lower among female patients. This was true across the United States, as well. The coronavirus is killing more men than women. The mortality from COVID-19 was higher in people older than 65 years and in people with underlying comorbidities, such as chronic lung disease, serious heart conditions, high blood pressure, excess weight, obesity, and diabetes. Global health experts estimated that 1.7 billion people of the global population have at least one underlying condition that puts them at increased risk for severe coronavirus disease. Do your genes predispose you to Covid-19? Blood types bear two kinds of saccharide molecules on the surface of red blood cells; A and B, -and each kind of molecule is produced by an enzyme, whose enzyme exists in two forms (A & B). A third gene variant encodes an inactive enzyme: type O. Each sugar A or B may act as an antigen. It can trigger antibodies that target the antigens it lacks. Type O blood is the best for antibody production, processing both anti-A and anti-B, and therefore offers the most protection. As to the mode of transmission, the virus is mostly transmitted through the respiratory tract. The infection occurs in the respiratory tract, and emissions from the tract are the propulsion mechanism in the environment and towards others. It is therefore important to understand, that not only the distance (social distancing), but also the concentration of the viral load, and of course, the time scales of exposures. The virus is never emitted in the air on its own. It is always in the mucosalivary secretion that is emitted from either breathing out, talking, coughing, or sneezing.

The SARS-CoV-2 global outbreak is one of a kind syndemic that occurs once in a century. Since this potent killer virus is new, and novel, not much of its mode of transmission, pathophysiology, clinical symptoms, and management was known in the early days of its outbreak. In view of this fact, public health experts, emergency medicine workers, clinicians, and critical care workers were scrambling for information. During the days that followed the initial discovery of this virus, there was a great rush for publication of articles on this topic. In a recent article in Science, Jeffrey Brainard reports, on how researchers face hurdles to evaluate, synthesize COVID-19 evidence at top speed.[17] The team analyzed more than 35,000 papers and reprints about COVID-19 in a database called Epistemonikos. Some of the revelations are unbelievable. For example, an unpublished analysis of some 240 reviews, about drug treatments for the disease found, 95% were already out of date. According to these investigators, a high percentage of COVID-19 reviews were found, to be incomplete or irrelevant only months after publication, and this observation is unprecedented, and demonstrates the complexities of this pandemic. They also found that 53 reviews, dealt with the effectiveness of hydroxychloroquine, an antimalarial drug, which has been used to treat COVID-19. Although President Donald Trump and other political leaders have touted it as a remedy, the reviews have not found any evidence, for its

benefits so far. Confusions in the management of COVID-19 becomes quite evident when you just analyze the number of drugs that were administered (VIP Syndrome?) to the President of the USA when he contracted the COVID-19. The drugs included infusion of 8.4 grams of Regeneron monoclonal antibody cocktail, Remdesivir, Dexamethasone, Zinc, Vitamin D, Aspirin, Famotidine, and Melatonin.

Discussion

A new virus-associated disease was initially reported in China on 30th December 2019.[18] Early researchers generated virus genome sequences from 53 patients in Guangdong, China, using both metagenomic sequencing and multiplex PCR amplification, followed by nanopore sequencing.[19] Many countries are now investing efforts in genomic surveillance of SARS-CoV-2, and the GISAID public database has now reached, 25,995 full genomes at unprecedented speed.[20] "The U.S. is the World's leader in advanced rapid genome sequencing," This coordinated effort across our public, private, clinical, and academic public health laboratories, will play a vital role in understanding the transmission, evolution, and treatment of SARS-CoV-2," said US CDC Director, Robert Redfield. Researchers at the National Institutes of Health (NIH), USA, developed approaches, combining advanced machine learning methods, with well-established genome comparison techniques, to identify potential genomic determinants of pathogenicity of the high-CFR coronavirus strains.[21] The hypothesis being, -that the high-CFR virus strains are more pathogenic due to shared genomic determinants, that are absent in the low-CFR strains. These researchers found that within the nucleocapsid, which predicts high CFR for this virus, there were deletions and insertions resulting in a substantial enhancement of the motifs that determine nuclear localization, specifically, in high-CFR coronavirus. Genomewide Association (GA) Study of Severe COVID-19 revealed that the risk allele GA of rs11385942 was associated with reduced expression of CXCR6 and increased expression of SLC6A20, and LZTFL1 was strongly expressed in human lung cells. They also found that the frequency of the risk allele of the lead variant 3P21.31 was higher among patients, who received mechanical ventilation, than among those who received oxygen supplementation.[22]

Coronaviruses have positive-sense RNA genomes, consisting of six conserved proteins. The conserved proteins are the polyproteins pp1a and pp1b, which encompass multiple protein domains involved in various aspects of coronavirus genome replication, spike protein (S), envelope (E), membrane glycoprotein (M), and nucleocapsid phosphoprotein (N). The size of this virus is between 60 nanometers (nm) to a maximum of 140 nm. Respiratory droplets are typically 5-10 micrometers and each droplet may contain 250 virions, which means just normal talking can generate more than 750,000 virions. According to the experts, the infectious dose of SARS-CoV-2 is probably like SARS-CoV, approximately 300 virions. Masks have been recommended primarily, to reduce SARS-CoV-2 transmission, rather than reduce the dose of infectious particles. In the absence of reliable data from randomized studies, there seems to be lots of confusion, about the efficacy of masks in preventing transmission of this virus. It is encouraging, that data have emerged from the state of California, for instance, to change its public health messaging; "masks protect you and others." The Institute for Health Metrics and Evaluation (IHME), University of Washington, currently projects, that more than 360,000 Americans will die by the end of 2020. It does not have to be this way. Promoting the use of masks, social distancing, and contact tracing could still save 100,000 lives—saving lives does matter. Russian President Vladimir Putin has taken his most drastic measures yet, to curb the second wave of COVID-19. He ordered on Tuesday (October 27, 2020) a nationwide mask mandate (which becomes effective this week), as coronavirus cases spike worldwide. The country has the fourth-highest number of COVID-19 cases in the world, behind the US, India, and Brazil. The other three countries have not ordered a countrywide mask mandate.

In the high-CFR strain, the nucleocapsid protein and the spike protein were significantly enriched. The N protein is multifunctional, contributes to viral transcription efficiency and pathogenicity. The SARS-CoV-2 spike proteins bind the ACE2 host receptor with a 10 to 20-fold affinity compared to SARS-CoV and contain a polybasic furin cleavage site, resulting in a unique insert to SARS-CoV-2 that enhances infectivity. Cleavage of S generates a polybasic Arg-Arg-Ala-Arg C-terminal sequence on S1 and S2. Furthermore, their analysis revealed a four-amino acid insertion in the long connecting region between the fusion peptide of the spike protein, in all high-CFR viruses, but not in low-CFR ones. Yet another difference they noticed was, increased positive charge of the amino acids, comprising the Nuclear Localization Signals (NLSs), a known marker of NLS strength (20). Recent findings suggest the interaction of yet another receptor, called neruopilin-1(NRP1), and neuropilin 2 (NRP2) that facilitate the entry of this virus into cells. Neuropilin-1, known to bind furin-cleaved substrates, "significantly potentiates SARS-CoV-2 infectivity, and is blocked by a monoclonal blocking antibody against NRP1." Despite this knowledge, about the molecular rearrangements that modulate the transmission, pathogenicity, and severity of the coronavirus disease, little is known about the reasons for the disproportionality in the infectivity and case fatality rates among the countries across the world.

The spike protein is a type 1 transmembrane protein, comprising 1255 amino acids and seems to be the key to the host cell interactions. The virus has undergone significant mutations as it evolved worldwide. However, S Protein seems to be the key determinant of evolution, transmission, and virulence of SARS-CoV-2.[23] Coronavirus entry into host cells is mediated, by the transmembrane spike (S) glycoprotein, that forms homotrimers protruding from the viral surface.[24] This protein comprises two functional subunits, responsible for binding to the host cell receptor (S1subunit), and fusion of the viral and cellular membranes (S2 subunit). For all viruses of this group, S unit is further cleaved by host proteases, at the S2 site of the fusion peptide. Because of this mode of transmission, coronavirus entry into the host cell is a complex

process, that requires both receptor binding and proteolytic processing of the S protein, to promote virus-cell fusion.[25] Chinese researchers studied the variations in SARS-CoV-2 spike protein cell epitopes and glycosylation profiles during global transmission course of COVID-19 and concluded, "Our research offers a novel perspective on the distribution characteristics of the relatively high frequency of amino acid variations, the impacts of T and B cell epitope variants, and the conserved glycosylation sites of SARS-CoV-2 S-protein, during global transmission. The SARS-CoV-2 *S* gene encodes 22 N-linked glycan sequons per promoter, which likely play a role in protein folding and immune evasion. This knowledge will contribute significantly to the evaluation of the vaccine candidate immunogenicity, as well as monitoring of the potential consequences of glycosylation and cell epitope variations, in the process of viral transmission.[26]

SARS-CoV-2 entry into a cell involves the interaction of its spike protein with the cell's membrane-bound angiotensin-converting enzyme 2 (ACE2) which is cleaved by the transmembrane protease serine 2 (TMPRSS2), suggesting that co-expression of both genes is required for infection.[27] According to experts, there are four important enzymes that are essential for the pathogenesis; the S-protein that facilitates virus entry through the ACE2 to the host cell surface receptor, the major protease of CoV3Clpro, and the papain-like protease (PLpro) involved in the assembly of new viruses, and RNA-dependent polymerase (RdRp) that facilitates CoV RNA genome replication.[28] The processing and activation of coronavirus S-protein are critical, for the infectivity of the virus. The proprotein convertase family (PCs) is composed of nine serine-secreting proteases and is widely involved in regulating various biological processes in normal and disease states. According to the experts, the biological processing and activation of coronavirus S-protein to expose the reactive domain also explains partially the phenomenon of COVID-19 with severe cardiovascular damage. Key cell entry mechanism includes higher ACE2 (hACE2) binding affinity of the spike, to the receptor-binding domain—reduced dependence on target cell proteases for entry, due to pre-activation by convertase furin.[29] This dependence also makes the virus vulnerable to designer drug interventions.

Researchers from the Department of Statistics, University of Dhaka published a Meta-Analysis, on the prevalence of clinical manifestations and comorbidities of coronavirus infection.[30] Of the total of 33 eligible studies, including 7673 infected patients, the most prevalent clinical symptom was fever (84.49%), cough (56.39%), fatigue (33.65%), dyspnea (22.34%), sputum production (22.34%), and myalgia (16.26%). Other symptoms reported include, shortness of breath, diarrhea, headache, chest pain, vomiting, sore throat, poor appetite, loss of smell and taste, and chills. The most prevalent comorbidity was hypertension (20%), cardiovascular disease (11.9%), and diabetes (9.8%). Other less know comorbidities include, excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease, and cerebrovascular disease.[31-35] These viruses enter the nasal epithelial cells, using the surface spike (S) proteins, to bind a metalloprotease enzyme called, angiotensin enzyme 2 (ACE2), which serve as receptors for 2019-nCoV, on the bronchial epithelial cells and type 11 pneumocytes. Researchers have analyzed the ACE2 RNA expression profile at single-cell resolution. High ACE2 (hACE2) expression has been identified in type 11 alveolar cells of lung, esophagus, enterocytes of ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, bladder urothelial cells, fat cells, and vascular endothelial cells.

Following infection and viral replication, downregulation of ACE2 enzyme occurs, resulting in dysfunction of the angiotensin system, resulting in hypokalemia, vasoconstriction, and development of acute respiratory distress syndrome. The endothelium is the largest organ of the body, covering a large surface area, and reaching out to every tissue and organ. As such, the injury to the endothelium could introduce a cascade of events, leading to platelet activation, thrombin generation, and promotion of both thrombotic and thrombolytic events. Just to distinguish the term 'vascular disease' from the vascular damage and pathology observed in the severely ill Covid-19 patients, we refer to this condition as a 'disease of the blood vessels'. In the majority of cases, the severity of the coronavirus disease has been found to be associated with pre-existing comorbidities, which include metabolic diseases such as hypertension, obesity, diabetes, and vascular diseases. Those with such diseases, or with elevated risk factors for such diseases will have a compromised endothelium, favoring endothelial dysfunction. The infection of endothelium by SARS-CoV-2 seems to add to this problem, by further damaging the endothelium, causing dysfunction, disruption of vascular integrity, and endothelial cell death. These events lead to the exposure of thrombogenic basement membrane and results in the activation of thrombotic and clotting cascade. In view of these observations, critical care clinicians recommend aggressive anti-thrombotic and thrombolytic therapies in the management of acute COVID-19 cases.

There is considerable interest in developing interventions, to prevent the interaction of spike (S) proteins of SARS CoV-2 with ACE2 receptors. According to a Center for Disease Control (CDC) report, the hospitalization rate during the 4-week period (March 2020) was 4.6%.[26] Therefore, major intervention strategies for the treatment and management of coronavirus disease are aimed at less than 5% of the infected population. In this population, the intervention will depend primarily, on clinical manifestations diagnosed by the critical care physicians. Researchers are also working on the interventions, aimed at the prevention of lung injury, protection of endothelium from cytokine storm, and ways and means for promoting effective immune modulation. Phenotype-driven approach to immunomodulation may include anti-cytokine therapy for selective patients and immunostimulatory therapies in others.[36] Researchers from Iran have suggested, the use of mesenchymal stromal cells (MSCs), to combat cytokine storm in covid-patients.[37] They conclude, "In a number of studies, the administration of these cells has been beneficial for COVID-19 patients. Also, MSCs may be able to improve pulmonary fibrosis and lung function."

At the level of population, currently, in the absence of an effective vaccine, the only choice we have is to follow the best

public health practices such as social distancing, using face coverings, or masks, frequent hand washing with soap, contact tracing, and strict quarantine of covid-positive individuals. Taiwan being next door to the epicenter of the global pandemic (China), has done a marvelous job of containing the spread of this virus (443 cases, seven deaths). Singapore has been hailed as a 'winner' of its pandemic response (38, 965 cases and 25 deaths). South Korea's aggressive early response has kept its overall case-count to a minimum (0.02%), of the population (11, 902 cases; 276 deaths), compared to the US 9.24 million cases and 231,000 deaths. In an unprecedented move, the prestigious New England Journal of Medicine has published an editorial with the title, "Dying in a Leadership Vacuum."[38] It starts off with a critical statement, "With no good options to combat a novel pathogen, countries were forced to make bad choices about how to respond. Here in the United States, our leaders have failed that test. They have taken a crisis and turned it into a tragedy." "The responses of our nation's leaders have been consistently inadequate." "Our current leaders have undercut trust in science and in government, causing damage that will certainly outlast them." Furthermore, the US administration has shamefully politicized the premier institutions, such as FDA, CDC, NIH, and the WHO, and has undercut trust in science, and in these prestigious regulatory, and global public health platforms. The editorial concludes, "When it comes to the response to the largest public health crisis of our time, our current political leaders have demonstrated that they are dangerously incompetent. In our half-century experience in academia, we have never seen such a critical editorial, in a prominent journal like the New England Journal of Medicine.

Contrary to these observations, The New York Times (Oct 28, 2020) published an Opinion titled "How America Helped Defeat the Coronavirus (Just not in the United States)." The authors, Sanya Dosani and associates, discuss how the U.S Public health leaders and scientists, have been planning a catastrophe just like COVID-19 for decades, and, in typical American fashion, we didn't just write the pandemic playbook,- we exported it around the world." They conclude, "What we found doesn't change the fact that more than 220,000 Americans have died from COVID-19, but it sheds light on a part of the U.S. pandemic global response. that hasn't gotten a lot of attention: that America's decades of pandemic planning did save lives. Just not at home." Though the 'opinion' of these authors has been presented as a podcast or a video, it basically tells us an investigative story about, - how the American Science and Public Health knowledge was shared worldwide, and gave the wherewithal to various countries around the world, to prepare and fight the viral pandemics. They discuss the success of Vietnam (1173/35), Thailand (3783/59), Republic of Korea (26,271/482), which had the lowest SARS-CoV-2 infection and deaths. They also give credit to the pioneer global health expert Dr. Dennis Carroll, who serves as the Director, Global Virome Project, a global cooperative scientific initiative to massively lower the risk of harm from future viral outbreaks over 10 years. In 2009, after several years at USAID, Dr. Carroll created an agency program called PREDICT, which "tracks what the different viral threats that are in wildlife might look like, what underlying drivers would lead those threats to spill over into the human population."

In the absence of a cure, sensible medicine proposes a gentler, moderate, and humble view of available treatment options and their effectiveness in patients with COVID-19. The approach encourages clinicians, to elevate usual care, reduce unnecessary interventionism, and focus and rely on scientific rigor.[39] By and large, treatment options are based on clinical diagnosis- based treatments for observed symptoms. For patients with COVID-19, who are not hospitalized or who are hospitalized with moderate disease, but do not require supplemental oxygen, -National Institutes of Health (NIH, USA) panel does not recommend any specific antiviral or immunomodulatory therapy, for the treatment of coronavirus disease in these patients. For those hospitalized with severe conditions, the panel recommends Remdesivir 200 mg intravenously (IV) for 1 day followed by a 100 mg dose for four days or until hospital discharge. A combination of Remdesivir and dexamethasone 6 mg IV up to 10 days. As mentioned earlier, there are no US FDA-approved therapies, for the coronavirus disease treatment. Yet when the US president was found to test positive for COVID-19, the prestigious Walter Reed National Medical Center, gave him an infusion of (8.4 grams) an experimental cocktail of Regeneron's REGN-COV2 (REGN-EB3),-two monoclonal antibodies. In addition, (VIP Syndrome), he received both Remdesivir and dexamethasone. He also received zinc, vitamin D, the generic version of Pepcid, and aspirin. Not every patient with a moderate coronavirus disease can afford or will get this kind of treatment.

FDA has created a special emergency program for possible coronavirus therapies, the Coronavirus Treatment Acceleration Program (CTAP). Currently, there are 590 drug development programs in planning stages, 390 trials in review, and five authorized for emergency use—none approved for use in COVID-19 management. There is another challenge, -as mentioned earlier this virus attacks all the tissue, systems, and organs, therefore its infection is accompanied by multiple clinical symptoms. In view of these observations, there is a great opportunity for developing a series of interventions to manage all the associated clinical symptoms. While industry giants are transfixed by the high-stake race to develop a COVID-19 vaccine, an equal crucial competition is heating up, to produce targeted, neutralizing antibodies that could provide, an instant immunity boost against this virus.[40] Immunologist Dennis Burton, whose group at Scripps Research has isolated highly potent monoclonal antibodies against SARS-CoV-2, hopes to move this novel therapy into human studies. He is optimistic that monoclonals will protect people from infection for months with a single shot. Pandemic Prevention Platform (P3) at the Defense Advanced Research Project Agency has a novel approach, in which they aim to develop monoclonal antibodies, that can be made by the body itself, instead of in large fermentation tanks. The idea, which has not been tested in humans for COVID-19, is to inject a person with DNA or messenger RNA, which encodes the desired antibody, allowing their own cells to make it.

According to the most recent WHO report, there are more than 140 COVID-19 vaccine candidates under

development, with a number of these in Phase 3 trials. When a safe and effective vaccine is found, COVAX (led by WHO, GAVI, CEPI) will facilitate the equitable access and distribution of these vaccines, to protect people in all countries. Four COVID-19 vaccine candidates are in Phase 3 clinical testing in the United States, just over eight months after SARS-CoV-2 was identified. This is an unprecedented feat for the scientific community, made by decades of progress in vaccine technology. As of September 28, there are 40 vaccine candidates in human clinical trials. ChAdOx1 no CoV-19, a recombinant adenovirus vaccine developed by the University of Oxford entered human trial in April of 2020 in the UK. Ad5-nCoV, a vaccine developed by CanSino Biologics of Beijing Institute of Biotechnology, entered a human clinical trial in March of 2020. The vaccine "Gam-COVID-Vac," developed by Moscow's Gamaleya Institute, is an adenovirus-based vaccine like the Oxford vaccine. In addition, the second vaccine in Russia, EpiVac Corona, has also been granted regulatory approval. In terms of prevention of SARS-CoV-2, at the population level, there are just two options, other than hiding from the virus by following the best practices recommended by the public health experts. One approach is to hope for the development of herd immunity, and the other is to develop a safe and effective vaccine and vaccinate most of the population. According to the experts, both these approaches require at least 60% of the population to acquire reasonable immunity to the virus. Researchers from the School of Public Health, Imperial College of London, have reported that antibodies developed in response to SARS-CoV-2 infection, seem to fade away in significant proportions, in just 3 or 4 months. This is not at all the good news. Having said that, we need to remind the reader that doesn't mean that immunity, either induced by infection or by vaccination, is necessarily short-lived. Memory cells can indeed respond to and combat a new infection, as programmed by innate physiological responses.

Currently, there are at least 51 studies listed in the COVID-19 vaccine tracker of the Regulatory Affairs Professional Society (RAPS) site. The top ten entries which are under Phase 3 trial include Ad5-nCoV, a recombinant vaccine by CanSino Biologics (China); AZD1222, a replication-deficient adenovirus vector vaccine (The University of Oxford, the Jenner Institute); CoronaVac by Sinovac; JNJ-78436735, a non-replicating viral vector by Johnson and Johnson; mRNA-1273, an mRNA based vaccine by Moderna; an unnamed inactivated vaccine by Wuhan Institute of Biological Products; NVX-CoV2373, a nanoparticle vaccine by Novavax. There are several new entries in Phase 2/3 trials including, BCG vaccine by the University of Melbourne and Mass. General Hospital, Boston; BNT162 mRNA-based vaccine by Pfizer, BioNtech; and Covaxin, an inactivated vaccine by Bharat Biotech, National Institute of Virology, India. According to a recent article in the New Engl J Med,[41] confidence in any COVID-19 vaccine that is made available under an emergency authorization (EUA), will depend on the rigor of the clinical criteria, including the duration of follow-up, safety, and efficacy of the vaccine. With Phase 3 clinical trials of COVID-19 vaccine underway, safety and efficacy data will be provided, to the FDA soon after they are compiled.[42] Emergency Use Authorization will be made by the FDA's Center for Biologics Evaluation and Research (CBER). The decision of this branch of the FDA has been approved by the Vaccines and Related Biological Products Advisory Committee (VRBPAC). In a short overview like this, on a complex topic like the COVID-19 syndemic, it is difficult to cover all aspects of the disease. We urge readers to refer to original articles, reviews and professional guidelines and COVID-19 resources.[22,43-53]

Conclusion

SARS-CoV-2-2019—the most pathogenic killer virus—has created an unprecedented, once in a century syndemic. Currently, global COVID-19 positive cases exceed 43,623,111 with 1,161,311 deaths. In the most advanced nation, the US, the COVID-19 positive cases exceed 9.2 million with 230,000 deaths. According to the experts, the coronavirus pandemic is the greatest threat, to prosperity and well-being, the US has encountered since the Great Depression. This is true for the other nations as well. This observation has led Harvard Economists, to estimate the collective cost of this pandemic, and publish their viewpoint in JAMA—"The COVID-19 Pandemic and the $16 Trillion Virus."[10] Coronaviruses are relatively large viruses (125 nanometers) with over 29, 000 genetic bases. They are bestowed with a genomic proof-reading mechanism, which keeps the virus from accumulating unwanted mutations. Analysis of 48,635 samples, confirms a low mutation rate of the virus, with an average of 7.23 mutations per sample. Further studies combining genomic details, with epidemiological information and clinical features of COVID-19 patients, may be extremely useful to identify strategies and therapies that can help to reduce the burden of this disease. For instance, one study has shown that the D614G mutation in the Spike protein may be associated with higher case fatality rates. These viruses continue to evolve, surely new features will emerge, or mutate alongside the genomic sequences, with clinical and pharmacological repercussions. Constant monitoring of mutations, therefore, will also be pivotal in tracking the movement of virus, between individuals and across geographical areas.

The virus latches onto a receptor called ACE2, which is found on the lining of the arteries and veins, which are the major supply routes, to all the organs of the body. Yet another enzyme, 'Furin" also seems to play a role in cleaving the viral spike protein. Both enzymes ACE2 and furin are abundant throughout the body, and facilitate the transmission of the virus from cell to cell, as well as person to person. Furin is known to be involved in the cleavage of a wide variety of proteins and is expressed ubiquitously. Recent findings suggest yet another receptor, one called neuropilin-1 facilitates virus entry into cells. Once the spike protein is attached, the internalization of the virus is promoted by hemagglutinin cleavage, modulated by the TMPRSS2, a cell surface-expressed protein by epithelial cells. Once the virions thus released fuse with the membrane, ACE 2 expression seems to get downgraded, resulting in excess production of angiotensin, and enhancing

oxidative stress mechanisms. Of the total of 33 eligible studies, including 7673 infected patients, the most prevalent clinical symptom was fever (84.49%), cough (56.39%), fatigue (33.65%), dyspnea (22.34%), sputum production (22.34%), and myalgia (16.26%). Other symptoms reported include, shortness of breath, diarrhea, headache, chest pain, vomiting, sore throat, poor appetite, loss of smell and taste, and chills. The most prevalent comorbidity was hypertension (20%), cardiovascular disease (11.9%), and diabetes (9.8%). Other less know comorbidities include, excess weight, obesity, chronic kidney disease, chronic liver disease, chronic pulmonary disease, and cerebrovascular diseases.

By and large, the treatment options for the effective management of COVID-19 positive individuals are clinical diagnosis-based and dependent on observed clinical symptoms. For patients with COVID-19, who are not hospitalized or who are hospitalized with moderate disease, but do not require supplemental oxygen, the National Institutes of Health (NIH, USA) panel does not recommend any specific antiviral or immunomodulatory therapy, for the treatment of coronavirus disease in these patients. In the eight months that have passed since the outbreak of this novel virus, emergency medicine staff, critical care clinicians, and other health care experts have learned a lot about the transmission, transfection, pathogenicity, and the role of preexisting health conditions, in enhancing the severity of this disease. This collective knowledge has helped the health care workers, to provide better care for the COVID-19 positive individuals. In the US, 4 vaccine candidates are in Phase 3 clinical trial, with initial results expected soon. There is considerable hesitation about receiving COVID-19 vaccination in the general public. Reasons include, the novelty and rapid development, as well as politicization of the pandemic, and inconsistent messages from scientists and government leaders. It is critical that clinicians stay well informed about emerging data, safety and efficacy of drugs, as well as these vaccines so that they can help patients make sound decisions.

Finally, we would like to encourage readers to watch the video released by the authors of the New York Times 'opinion' titled, "How America Helped Defeat the Coronavirus (Just not in the United States)" and the editorial published by the New England Journal of Medicine titled "Dying in a Leadership Vacuum."

References

1. Singer M, Bulled N, Ostrach B, Mendenhall E. Syndemics and the biosocial conception of health. Lancet. 2017 Mar 4;389(10072):941-950. doi: 10.1016/S0140-6736(17)30003-X.
2. Rao GHR. Coronavirus Disease Pandemic: A Public Health Perspective. J Med and Healthcare. 2020; 2(4):1-7.
3. Rao GHR. COVID-19 and Cardiometabolic Disease. EC Cardiol. 2020;7.6:08-12.
4. Rao GHR. Coronavirus Disease and Acute Vascular Events. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620929091. doi: 10.1177/1076029620929091.
5. Rao GHR. Coronavirus Disease, Comorbidities, and Clinical Manifestations. Acta Sci Pharmacology. 2020;1.8
6. Rao GHR. Coronavirus Disease (Covid-19): A Disease of the Vascular Endothelium. Ser Cardiol Res. 2020;2(1):23-27
7. Rao GHR: Coronavirus Disease Transmission, Vascular Dysfunction and Pathology J Cardiol Res Rev & Rep. 2020;1(3):1-4
8. Rao GHR. Excess Weight, Obesity, Diabetes and Coronavirus Disease. Arch Diab & Obesity 3(1)-2020. MS ID.000152. doi: 10.32474/ADO.2020.03.000152.
9. Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics. Emerg Infect Dis. 2006 Jan;12(1):15-22. doi: 10.3201/eid1201.050979.
10. Cutler DM, Summers LH. The COVID-19 Pandemic and the $16 Trillion Virus. JAMA. 2020 Oct 20;324(15):1495-1496. doi: 10.1001/jama.2020.19759.
11. Brandsma E, Verhagen HJMP, van de Laar TJW, Claas ECJ, Cornelissen M, van den Akker E. Rapid, sensitive and specific SARS coronavirus-2 detection: a multi-center comparison between standard qRT-PCR and CRISPR based DETECTR. J Infect Dis. 2020 Oct 10:jiaa641. doi: 10.1093/infdis/jiaa641.
12. Slavitt A. Science is Needed to Rescue the Nation from Covid-19, but Not Just Traditional Biomedical Science. JAMA Forum|COVID-19. Available at: https://jamanetwork.com/channels/health-forum/fullarticle/2771804
13. Burki T. The origin of SARS-CoV-2. Lancet Infect Dis. 2020 Sep;20(9):1018-1019. doi: 10.1016/S1473-3099(20)30641-1.
14. Cohen J. Chinese researchers reveal draft genome of virus implicated in Wuhan pneumonia outbreak. Science. 2020. doi:10.1126/science.aba8829.
15. Wang H, Li X, Li T, Zhang S, Wang L, Wu X, Liu J. The genetic sequence, origin, and diagnosis of SARS-CoV-2. Eur J Clin Microbiol Infect Dis. 2020 Sep;39(9):1629-1635. doi: 10.1007/s10096-020-03899-4.
16. Koyama T, Platt D, Parida L. Variant analysis of SARS-CoV-2 genomes. Bull WHO. 2020; 98:495-504.
17. Brainard J. Researchers face hurdles to evaluate, synthesize COVID-19 evidence at top speed. Health, Scientific Community: Coronavirus; Science. 2020 doi:10.1126/science.abf1761.
18. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature. 2020 Mar;579(7798):265-269. doi: 10.1038/s41586-020-2008-3.
19. Lu J, du Plessis L, Liu Z, Hill V, Kang M, Lin H, et al. Genomic Epidemiology of SARS-CoV-2 in Guangdong Province, China. Cell. 2020 May 28;181(5):997-1003.e9. doi: 10.1016/j.cell.2020.04.023.
20. Lam TT. Tracking the Genomic Footprints of SARS-CoV-2 Transmission. Trends Genet. 2020 Aug;36(8):544-546. doi: 10.1016/j.tig.2020.05.009.
21. Gussow AB, Auslander N, Faure G, Wolf YI, Zhang F, Koonin EV. Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses. Proc Natl Acad Sci U S A. 2020 Jun 30;117(26):15193-15199. doi: 10.1073/pnas.2008176117.

Contact Information: *Emeritus Professor Gundu H.R. Rao, Laboratory Medicine and Pathology, Director, Thrombosis Research, Lillehei Heart Institute, University of Minnesota. 12500 Park Potomac Ave, Unit 3 06N, Potomac, MD 20854. E-mail: gundurao9@gmail.com*

22. Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, et al. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. N Engl J Med. 2020 Oct 15;383(16):1522-1534. doi: 10.1056/NEJMoa2020283.
23. Abdullahi IN, Emeribe AU, Ajayi OA, Oderinde BS, Amadu DO, Osuji AI. Implications of SARS-CoV-2 genetic diversity and mutations on pathogenicity of the COVID-19 and biomedical interventions. J Taibah Univ Med Sci. 2020 Aug;15(4):258-264. doi: 10.1016/j.jtumed.2020.06.005.
24. Tortorici MA, Veesler D. Structural insights into coronavirus entry. Adv Virus Res. 2019;105:93-116. doi: 10.1016/bs.aivir.2019.08.002.
25. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020 Apr 16;181(2):281-292.e6. doi: 10.1016/j.cell.2020.02.058.
26. Xu W, Wang M, Yu D, Zhang X. Variations in SARS-CoV-2 Spike Protein Cell Epitopes and Glycosylation Profiles During Global Transmission Course of COVID-19. Front Immunol. 2020 Sep 4;11:565278. doi: 10.3389/fimmu.2020.565278.
27. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052.
28. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019-nCoV. Chembiochem. 2020 Mar 2;21(5):730-738. doi: 10.1002/cbic.202000047.
29. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020 May 26;117(21):11727-11734. doi: 10.1073/pnas.2003138117.
30. Noor FM, Islam M. Prevalence of Clinical Manifestations and Comorbidities of Coronavirus (COVID-19) Infection: A Meta-Analysis. Fortune J Health Sci. 2020;3(1):55-97.
31. Rao GHR. Coronavirus Disease and Acute Vascular Events. Clin Appl Thromb Hemost. 2020 Jan-Dec;26:1076029620929091. doi: 10.1177/1076029620929091.
32. Rao GHR. COVID-19 and Cardiometabolic Diseases: Guest Editorial. EC Cardiol. 2020;7(6):08-12.
33. Rao GHR. Coronavirus (COVID-19), Comorbidities, and Acute Vascular Events: Guest Editorial. EC Clinical Case Reports. 2020;3(6):87-91.
34. Rao GHR. Coronavirus Disease 2019 (COVID-19), Comorbidities, and Clinical Manifestations: Guest Editorial. EC Diab Met Res. 2020;4(8):27-33.
35. Rao GHR: Coronavirus Disease (COVID-19): A Disease of the Vascular Endothelium. Series Cardiology Res. 2020;2(1):23-27.
36. Hall MW, Joshi I, Leal L, Ooi EE. Immune modulation in COVID-19: Strategic considerations for personalized therapeutic intervention. Clin Infect Dis. 2020 Jul 1:ciaa904. doi: 10.1093/cid/ciaa904.
37. Kavianpour M, Saleh M, Verdi J. The role of mesenchymal stromal cells in immune modulation of COVID-19: focus on cytokine storm. Stem Cell Res Ther. 2020 Sep 18;11(1):404. doi: 10.1186/s13287-020-01849-7.
38. Editors. Dying in a Leadership Vacuum. N Engl J Med. 2020 Oct 8;383(15):1479-1480. doi: 10.1056/NEJMe2029812.
39. Seymour CW, McCreary EK, Stegenga J. Sensible Medicine-Balancing Intervention and Inaction During the COVID-19 Pandemic. JAMA. 2020 Oct 15. doi: 10.1001/jama.2020.20271.
40. Cohen J. Designer antibodies could battle COVID-19 before vaccines arrive. Science. 2020. doi: 10.1126/science. abe1740
41. Krause PR, Gruber MF. Emergency Use Authorization of Covid Vaccines - Safety and Efficacy Follow-up Considerations. N Engl J Med. 2020 Nov 5;383(19):e107. doi: 10.1056/NEJMp2031373.
42. Schwartz JL. Evaluating and Deploying Covid-19 Vaccines - The Importance of Transparency, Scientific Integrity, and Public Trust. N Engl J Med. 2020 Oct 29;383(18):1703-1705. doi: 10.1056/NEJMp2026393.
43. Lee EC, Wada NI, Grabowski MK, Gurley ES, Lessler J. The engines of SARS-CoV-2 spread. Science. 2020 Oct 23;370(6515):406-407. doi: 10.1126/science.abd8755.
44. Beck DB, Aksentijevich I. Susceptibility to severe COVID-19. Science. 2020 Oct 23;370(6515):404-405. doi: 10.1126/science.abe7591.
45. Daly JL, Simonetti B, Klein K, Chen KE, Williamson MK, Antón-Plágaro C, et al. Neuropilin-1 is a host factor for SARS-CoV-2 infection. Science. 2020 Nov 13;370(6518):861-865. doi: 10.1126/science.abd3072.
46. Cantuti-Castelvetri L, Ojha R, Pedro LD, Djannatian M, Franz J, Kuivanen S, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020 Nov 13;370(6518):856-860. doi: 10.1126/science.abd2985.
47. Toelzer C, Gupta K, Yadav SKN, Borucu U, Davidson AD, Kavanagh Williamson M, et al. C. Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein. Science. 2020 Nov 6;370(6517):725-730. doi: 10.1126/science.abd3255.
48. Matheson NJ, Lehner PJ. How does SARS-CoV-2 cause COVID-19? Science. 2020 Jul 31;369(6503):510-511. doi: 10.1126/science.abc6156.
49. V'kovski P, Kratzel A, Steiner S, Stalder H, Thiel V. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol. 2020 Oct 28:1–16. doi: 10.1038/s41579-020-00468-6.
50. Masters PS. The molecular biology of coronaviruses. Adv Virus Res. 2006;66:193-292. doi: 10.1016/S0065-3527(06)66005-3.
51. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci U S A. 2020 May 26;117(21):11727-11734. doi: 10.1073/pnas.2003138117.
52. Kondo T, Iwatani Y, Matsuoka K, Fujino T, Umemoto S, Yokomaku Y, et al. Antibody-like proteins that capture and neutralize SARS-CoV-2. Sci Adv. 2020 Oct 14;6(42):eabd3916. doi: 10.1126/sciadv.abd3916.
53. Kamps BS, Hoffman. COVID Reference. 2020.4 Available at: https://amedeo.com/CovidReference04.pdf