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Covid-9: A Review about One of the Worst Known Pandemics of the Century

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Abstract

The current outbreak of the novel coronavirus SARS-COV-2 known as COVID-19 is one of the biggest known pandemics to have occurred. Much of the information regarding the SARS-COV 2 has been obtained owing to its similarities to the SARS virus. The spike proteins of the virus attack the ACE 2 receptors present mainly in the respiratory tract. The human body reacts vigorously to the infection by releasing a vast amount of interferon and interleukins which transform into a cytokine storm leading to an acute respiratory distress syndrome. Studies show that people with comorbidities are subject to a greater risk of catching the infection. A large section of these people has underlying cardiovascular diseases and blood pressure. An interesting hypothesis about ACE inhibitors possibly up regulating the ACE 2 receptors and exposing patients to a greater risk is also being studied upon. While the search for a vaccine for COVID-19 is ongoing, convalescent plasma therapy has emerged as an effective therapy for severely affected patients. Anti-viral drugs such as chloroquine, hydroxychloroquine, and remdesivir are also being tried as potential medications. Scientists have advised the intake of vitamin C and vitamin D in adequate doses daily, as studies have shown patients taking these vitamin supplements have lesser risks to catching pneumonia. This review article takes a deep look at how the SARS-COV 2 virus works, its primary symptoms while also briefing about the prophylaxis and medications.

Keywords: Coronavirus; ACE2 receptors; Alveolar edema; RNA vaccine; Convalescent plasma; Remdesivir

Introduction

Coronaviruses are a large family of viruses that can cause respiratory tract infections in humans. The previous major outbreaks of coronavirus diseases include the Severe Acute Respiratory Syndrome (SARS) in 2003 and the Middle East Respiratory Syndrome (MERS) in 2012. The SARS outbreak originated in Shunde, China affecting about 8000 people and having a death rate of 9.2%. The MERS outbreak had a greater fatality rate of about 37% but was largely confined to the middle east countries, originating in Jeddah, Saudi Arabia and infecting about 2500 people. The current outbreak of the novel coronavirus SARS-COV-2, known as COVID-19 is one of the biggest known pandemics to have occurred. Originating in the Hubei province of the People's Republic of China, it has killed close to 384,000 people all over the world with a whopping 6.5 million cases as of writing. On 30th January 2020, the WHO Emergency Committee declared a global health emergency. As per the information revealed by the WHO, the virus primarily spreads from person to person through respiratory droplets when a person coughs or sneezes. Hence, it is mandatory to maintain a distance of at least 6 feet and regularly wash and clean oneself. The most common symptoms of COVID-19 include fever, dry cough, and shortness of breath. The severely ill patients have trouble in breathing and may require mechanical ventilators. Other symptoms which are less common include headaches, pains, diarrhea, loss of taste or smell or a skin rash and discoloration of hands and toes. Currently the fatality rate stands at 6.8% and majority of the deceased are old aged people having comorbidities. The people having underlying cardiovascular diseases, diabetes, blood pressure, lung diseases or cancer are at an increased risk to catch the infection as their body's immune system is weakened. There are no current vaccines or medications to treat the disease. Since, this is a novel coronavirus, a lot of the research is new and randomized trials are being carried out in almost all the countries. This article provides a brief overview of our current situation highlighting the information and current developments made regarding the virus.

The SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) which has caused the COVID-19 pandemic belongs to the group of beta-coronavirus and it resembles closely to the SARS virus. The problem, however, is that it has 20 times more affinity than the SARS virus. It is from this resemblance that we have derived most of the information. The viruses are mostly enveloped by proteins or have a protein coat. The shape of SARS-COV-2 is spherical with projections shaped in the form of a crown known as Spike proteins. It is these spike proteins that help the virus to bind to the receptors of the host cell. It recognizes the ACE2 (Angiotensin

Converting Enzyme Receptors 2) which is mostly present in the lungs, heart, and intestines. The site of infection of the virus is mostly the respiratory tracts of humans. The alveoli inside the lungs are like air sacs where the exchange of gases takes place inside the body. The SARS-COV-2 virus attacks these alveoli. It has an incubation period of 4-14 days. There are 2 types of cells on the walls of the alveoli- Type 1 Pneumocytes and Type 2 Pneumocytes. The type 1 pneumocytes help in the gaseous exchange whereas the type 2 pneumocytes produce surfactants that decrease the surface tension and prevent the collapsing of the alveoli which are bag-like structures.

Mechanism of Attack

The spike proteins on the surface of the virus attack the ACE2 receptors present on the Type 2 Pneumocytes. Once the virus membrane fuses with the host cell membrane (in this case the Type 2 Pneumocytes), the positive-sense single-stranded RNA (ssRNA) is released into the cells. It is now that the virus takes over the mechanism of the host cell and damages it. The positive-sense ssRNA use the host cells ribosomes (organelles inside a cell that help in the process of translation) and translate into polypeptides which in the presence of proteinases (enzymes which help in the synthesis of proteins) form the structural proteins of the new virus particles (like the envelope, spike, membrane proteins, etc). Some of these positive sense ssRNAs use the RNA dependent RNA Polymerase enzyme to produce more RNA which forms the genetic material of the new virus particle. Thus, the initial SARS-COV-2 virus replicates and makes multiple copies of itself within the host cell and gets released outside the host cell-damaging it.

Symptoms

Once a cell gets damaged inside our body, there are a lot of responses that get triggered and disrupt the normal functioning of the body. One such immediate response is the release of inflammatory mediators which stimulate the macrophages. The macrophages are a type of white blood cells (WBCs) in our body which fight infections and form a part of the defense mechanism of the body. The macrophages release another type of chemical called Interleukins which move into the surrounding blood capillaries and increase their permeability and lead to their dilation called vasodilation. This results in more and more fluid coming out of the capillaries and surrounding the alveoli. This is a natural defense mechanism of the body that recognizes the damaged alveolar cells as the target site of the virus and tries to fight off the virus. As a result, more and more WBCs are sent into these damaged alveoli. They release reactive oxygen species, proteins, and chemicals to fight the virus. They may kill a few virus particles but also end up destroying the pneumocyte cells. Moreover, the build-up of the fluids around the alveoli leads to a condition called alveolar edema where the fluids drown out the surfactants on the walls of the alveoli leading to an increase in surface tension ultimately resulting in the collapsing of the alveoli. Thus, the breathing becomes difficult and more work must be done to maintain a normal breathing pattern. This explains the restlessness symptoms and the breathing difficulties which COVID-19 patients experience. The condition is called hypoxemia. This hypoxemic condition tells the chemoreceptors about the low oxygen content in the arterial blood. The result of which leads to an increased heart rate.

As mentioned earlier, the macrophages are stimulated to release chemicals called interleukins. These interleukins namely interleukin-1 and interleukin-6 travel to the Central nervous system which constitutes the brain and the spinal cord. In the central nervous system, the hypothalamus controls most of the involuntary activities like body temperature, hunger, sleep cycle, etc. The high concentration of the interleukins stimulates the hypothalamus to increase the body temperature resulting in high fever which is generally considered to be above 100.4 degrees Fahrenheit.

The WBCs release a lot of reactive oxygen species, chemicals, proteins that kill the cells of the alveoli, and few virus particles. These settle down in the damaged alveoli as consolidate which is thrown out of the body as cough. Hence the cough symptoms, particularly the dry cough.

In some of the more serious infections, the ones that need intensive care, the inflammatory responses spread to the circulatory system of the body and produce the same effects. They lead to vasodilation of the capillaries resulting in a decrease in blood pressure and an increase in the permeability of the capillary walls. As a result, the blood volume decreases inside the capillaries and the fluid starts accumulation around the organs. The perfusion to multiple organs decreases and leads to multi-system organ failure or more technically septic shock. So, what started as an Acute Respiratory Distress Syndrome (ARDS) soon spreads into a Systemic Inflammatory Response Syndrome (SIRS). This may explain why people with multiple illnesses are more prone to the spread of the infection.

The risk posed to cardiovascular patients

It has been observed that most of the deaths due to COVID-19 have been to people aged 70 or more. A lot of these people, close to 30-40%, had extremely high blood pressure, diabetes, and other cardiovascular diseases. The people having high blood pressure are highly likely to be diagnosed with diabetes and vice versa.

The COVID-19 infection interferes with oxygen delivery to the various organs in the body. The oxygen exchange occurs in the alveoli in the lungs and the blood delivers this oxygen to the organs. So, having any ailment in either or both processes is more likely to cause multi-organ failure and this is the reason behind many of the deaths across the world.

High blood pressure may exert greater pressure on the finest of capillaries and the blood vessels in the body. This can be verified by examining the smallest blood vessels in the eyes of severely high blood pressure (BP) patients. It is natural that in the response to the infection our heart works harder and pumps blood with a lot more pressure in an already high BP patient causing further damage to the blood vessels, thus the

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amount of blood that needs to be delivered to the required organs is not met leading to multi-organ failure and death. High BP patients generally have more muscular hearts making them stiffer. As a result, the heart can contract well but do not necessarily relax properly. The relaxing phase known as the diastole helps in filling up the heath with blood. As the diastolic phase is affected, less blood is filled and hence less blood is pumped out which again complicates the amount required to be transported to various organs leading to their failure and death.

ACE inhibitors and COVID-19

The spike proteins of the coronavirus bind to the ACE2 receptors in our lungs. Any changes in the normal blood volume in the body are sensed by the RAAS (Renin-Angiotensin-Aldosterone) system where the kidney plays a key role. Our body is a wonderfully designed machine in which the abnormality in the functioning of one organ can be sensed by the other. In certain people when there is a low volume of blood flow or there is low blood pressure even by the slightest amount, the kidney releases an enzyme Renin which activates the angiotensin enzyme. This angiotensin 1 enzyme is further activated to angiotensin 2 by the ACE1 present in the lungs. Angiotensin 2 then goes to different target organs and increases the blood volume and the pressure. When this blood volume and the blood pressure are restored to normal, negative feedback tells the kidney to stop the release of renin [1].

This is manageable for an acute period but when this negative feedback is non-functional or there are certain other abnormalities, the heart pumps more than normal and leads to an increase in blood pressure [2]. Since high blood pressure is a quite common illness, a lot of the people are given ACE inhibitors which restrict the role ACE leading to less production of angiotensin 2. A recent study showed that in some ways the ACE inhibitors lead to a downregulation of ACE1 which is responsible for the production of angiotensin but leads to an up-regulation of ACE2 which acts as the receptors of the spike protein of coronavirus. Another study in China stated that the more severe cases which ultimately died were highly aged, suffered from ailments like heart problems, diabetes, and were taking a lot of ACE inhibitors. From some of the urine studies, it was found that they had a higher concentration of ACE2 [3].

This, however, should not mean that we stop taking the ACE inhibitors as there is no conducive evidence to show that the greater concentration of ACE2 found in some of the patients was primarily due to them taking a lot of ACE inhibitors. It is still just a hypothesis which is being worked at [4]. Moreover, stopping the ACE inhibitor medication abruptly may lead to greater complexities and the body may respond unhealthily which further increases the risk of infection. The major factor in all the deaths has been the age factor and primarily the body not responding to the infection in inadequate ways so unless a severe infection or a doctor's advice one should not stop any medication they are on, abruptly.

Prophylaxis and medications

Convalescent plasma therapy: While serious efforts are being made in the hope of developing a vaccine against COVID-19, scientists and doctors have turned to administer convalescent plasma for temporary treatment. Convalescent plasma therapy refers to the process of transfusing plasma containing the necessary antibodies against the SARS-COV-2 virus from an individual who has fully recovered from the COVID-19 infection into the blood of an active patient. This is a means of passive immunity where we are injecting the pre-formed antibodies into an infected patient. The convalescent plasma therapy has been in use for centuries, mostly when a novel infection spreads and there is no approved measure to treat the infection or when a vaccine is not ready yet. Historically, this therapy has been in use in the 2 previous coronavirus epidemics, SARS in 2003 and MERS in 2012. Previous experience shows a favorable outcome with the patients administered with convalescent plasma healing better [5].

When the antibodies are administered from an already recovered patient to an ill patient, they can work in various ways. The antibody can directly bind to the pathogen thereby neutralizing it or activate other antibody-mediated pathways such as the complement pathway. The chances of success are more pronounced if plasma therapy is administered during the early onset of symptoms. However, proven antiviral drugs and vaccines offer a more effective and durable treatment of the infection.

The first promising report of the plasma therapy came from a pilot study of 10 patients in China. The patients showed an improvement in symptoms within 1-3 days of administering convalescent plasma. Further 7 of those patients showed undetectable traces of the virus after treatment. Since the study constitutes a small sample size, further randomized trials need to be done to come to any sort of conclusion. As many as 5 clinical trials have been proposed, targeting patients at different stages of the infection [6]. In the same pilot study carried out in China, it was observed that a dose of 200 mL of convalescent plasma (CP) transfusion significantly improved the symptoms in an average of 3 days. Patients infected with SARS-COV 2 generally show a severe form of pneumonia with highly decreased lymphocyte count in the bloodstream and high cytokine levels particularly in the alveoli of the lungs. It was observed that after a successful CP transfusion, the oxygen saturation and the lymphocyte count were restored close to normal and the inflammations of the immune system were significantly improved by the neutralizing antibodies from the donor. Thus, CP transfusion has emerged as a very effective short term solution to the pandemic and more importantly gives us time in the search of antiviral drugs and vaccines which could be used as a permanent therapy against the virus [7].

One of the major pre-requisites is to find an eligible donor having sufficient antibody titer for donation. In our earlier fights against coronavirus such as that in MERS, the neutralizing antibody titer level was 1:80. The antibodies lost their effectiveness and were gradually depleted within 3

months. In the case of SARS, it was further less. Recent studies of COVID-19, however, show that the levels of neutralizing antibody titer were higher than those used in the treatment of MERS. Thus, it is important to use CP transfusions from recently recovered patients.

Risks: Since the CP transfusion in case of COVID-19 is like the plasma transfusion practiced in case of other illness, the risks associated are also similar. Firstly, there is always a chance of immunogenic complications in case of a mismatch of the blood types. Other hazards include allergic reactions and the potential transmission of the viral pathogen. This is however extremely rare according to the studies carried out so far and is less than 1%. The blood is subjected to methylene blue photochemistry to inactivate any residual virus and to maintain an exceedingly high level of antibody titer. Particularly in the case of elderly patients and those having cardiovascular ailments, transfusion-related circulatory overload (TACO) may be a risk and the fluid volume must be managed well. Those patients who have a severe case of COVID-19 or have underlying pulmonary ailments, transfusion-related acute injury, or TRALI is also a potential risk. Apart from the above, there is always a risk of antibody-dependent infection enhancement or ADE. ADE is a condition where the antibodies which developed because of a previous infection or ailment cause complications on reaction with a different viral serotype. It is worth mentioning as ADE was found in SARS-COV infection in-vitro. Fortunately, this was not the case in any of the patients treated with CP transfusion so far, maybe owing to timely treatment and high levels of neutralizing antibody titer [6].

Chloroquine and Hydroxy-chloroquine medications: Chloroquine and hydroxychloroquine have been known to be incredibly good antiviral drugs. They work in 3 ways,

- The virus needs an acidic environment to replicate its genetic material. Both Chloroquine and Hydroxychloroquine have an alkaline group which raises the pH (making it alkaline) inside the host cell and prevents viral replication.
- Chloroquine is known to act as a conduit for the zinc ions to come into the cell. It is called a zinc ionophore. Zinc blocks the activity of the RNA dependent RNA Polymerase which helps in making new RNA strands from the positive sense ssRNA of the SARS-COV-2 virus.
- Lastly, according to a recent study it was found that the Chloroquine and Hydroxychloroquine block the sialic acid receptors which are small sugar moieties acting as receptors for the spike protein of the SARS-COV-2 virus.

Since these medications have been used for a long-time treating disease like malaria, lupus, rheumatoid arthritis the thought that they could be used in the COVID-19 patients was interesting to the researchers. However, till now nothing conclusive has yet been confirmed. We have a lot of conflicting studies that have yielded completely contrasting results when tested in vitro and in vivo.

Concerning the present coronavirus, we have a controversial French study. A sample of 42 patients suffering from mild coronavirus, having an average age of 45 years were tested. 26 of them were administered 600 mg of Hydroxychloroquine for 6 days and rest 16 were not given this medication and were observed as control. 6 of the 26 patients were given the antibiotic azithromycin along with hydroxychloroquine. When they were observed after 6 days, it was found that 70% of the patients who were given the medication tested negative while only 12.5% of the patients who were not given any medication tested negative. The problem arose when it was found that out of the 26 patients, the data of 6 patients were not monitored as they could not complete the medication. Out of them, 1 patient died midway and 2 were taken into intensive care. The interesting thing about the person who died was that he tested negative for coronavirus. So, it could not be concluded whether he died because of the side effects of the drug or there were other underlying conditions. Now, as these trials are very small-scale trials, they cannot be considered conclusive. Presently the US has started a large-scale trial for checking the reliability of these medications as regards the COVID-19 infection and the FDA is hopeful we can get the results of the trial within a month.

Although the severe side effects of using chloroquine and hydroxychloroquine tablets are extremely rare, we do not know yet how they would impact a COVID-19 patient. Few studies say that long term usage can cause retinal damage and nerve and muscle toxicity in some rare cases. A French study conducted a trial of 25 patients having cardiomyopathy and using the chloroquine medication. Later it was found that almost half of them died and the rest showed improvements in taking away the medication. It is known to increase the QT interval of the heartbeat causing cardiac arrhythmia and weakening of the heart. The plus point on our behalf with this argument is that if we use these medications for combating the COVID-19 infection, we will require the antiviral drug only for a small period. So, the long-term ill-effects may be overcome.

Recently, the Indian Council of Medical Research (ICMR) released a report based on 3 studies which allows the frontline workers to take Hydroxychloroquine tablets as a prophylactic or preventive measure. The advisory released suggests that the surveillance workers, paramilitary, police personnel as well as the medical staff should start taking the pills as a preventive measure. The report also says that in case the people taking the pill experience any rare side effects, they should stop the medication immediately. The advisory also states that in rare cases, symptoms like blurring of vision may be experienced which improves upon discontinuing the pills. The study was conducted on 1323 healthcare workers and the rare side effects such as nausea was found in 8.9 percent of the workers, abdominal pain in 7.3 percent workers, vomiting in 1.5 percent, low blood sugar in 1.7 percent and cardiovascular effects in 1.9 percent of the workers.

Since the drug interferes with the viral replication within the cells and acts as a zinc ionophore, taking hydroxychloroquine pills along with zinc early could act as a prophylactic measure. This however would be of little to no use once the infection has spread causing severe conditions of the disease. Maybe this explains why the medication has had some success when

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administered early while it has not been effective in case of severe conditions. Research regarding the clinical use of this drug with regards to COVID-19 still has not yielded positive results and we must wait for further reports before depending solely on the use of this drug.

Vitamin D: The discussion regarding the effectiveness of Vitamin D supplements concerning COVID 19 infections comes from the studies showing the patients suffering from severe pneumonia had less amount of vitamin D in their bodies. Although vitamin D does not directly kill or protect us from the virus, it is insufficiency is associated with increase susceptibility to infections like acute respiratory tract infections. It has been shown that adequate levels of vitamin D in the body decreases the risk of respiratory infections. The recommended daily intake of Vitamin D is 1000-2000 IU per day. Animal food like fish, cod liver oil, eggs, and fortified food like milk, cereals, yogurts, etc. are rich sources of vitamin D.

Vitamin D receptors are present in many immunological cells. It works by upregulating the levels of immune system proteins like Cathelicidins and Beta-defensins. These proteins have anti-viral, anti-bacterial, and anti-fungal properties. They work by reducing the cytokine storm, reduce the T-helper cell inflammatory cytokine production, and regulate the interleukin levels all of which are a part of the response mechanism on the infection of the virus. Hence, the people taking the required amount of vitamin D in their diet will have an innate ability to fight the infection better as compared to the ones who are deficient in it.

Remdesivir: Remdesivir as an anti-viral drug was used during the Ebola outbreak. Although it did not yield successful results, its potential as a therapeutic anti-viral drug against SARS-COV 2 is much talked about. Various clinical trials are currently underway and there have been some successful results. It is generally given through IV transfusions and not orally. It is administered in its inactive form which becomes active once it goes into the body's metabolism. Its active form is an analog of the nucleoside adenosine. Since it is an analog of the nucleotide which is a part of the structure of RNA molecule, the viral RNA during its synthesis often gets tricked and remdesivir attaches to the RNA strand at the position of adenosine inhibiting the activity of RNA Polymerase. This blocks the effectiveness of the entire RNA strand of the virus. Recent studies have shown that remdesivir has led to a decrease in viral RNA load.

One of the studies took a sample of 53 patients from across countries of the USA, France, Germany, Italy, and gave them doses of 200 mg of remdesivir for the first day and a further 100 mg for the next 9 days. The results showed that 36 of the 53 patients showed an improvement in the symptoms whereas 8 of the patients had worsening of their conditions. Out of those 8, 7 patients died. Another trial carried out by Gilead too showed a positive result with improvement in conditions, however, remdesivir failed a test conducted in China.

Outlook into the future: The worldwide lockdown has given us time to carry out randomized trials on various anti-viral drugs. By reverting to the practice of social distancing and complete shutdowns, we can expect the spread of the infection to minimize. About 100 countries in the world have taken the initiative to develop a vaccine in record amount of time. Efforts are being made to develop an RNA vaccine instead of using attenuated or weakened form of the virus as is the case of conventional vaccines developed over time. In this process, the genome of the spike protein is identified and encrypted into the mRNA molecule. This mRNA molecule is then injected into humans. It is relatively easy to encode mRNA strands with any nucleic acid sequence and the variations can be easy to make in case of mutations. It is a new approach and is expected to save a lot of time.

US based company Moderna has had its mRNA vaccine candidate mRNA-1273 fast tracked by the FDA for second phase of human trails. In other positive news, Oxford University vaccine named ChAdO×1 nCoV-19 has shown promising signs in Macaques monkeys. Similar research carried out by Israel based Tel Aviv university aims at developing a vaccine which targets a specific part of the spike protein which causes the infection and not the entire protein in order to minimize the risk of antibody enhancement reactions (ADE).

The positive developments do indicate that the vaccine might be ready in the next year or so. Although the possibility of a re-infection is not proved yet, certain models do predict that the virus may not go away completely. Few have also looked at the possibility of second or third peaks in the later part of the year. While few countries like New-Zealand have had no cases since the end of April, countries like Russia and India are experiencing a late surge in the number of cases inspite of the lockdown. Immunization seems to be our only hope of complete immunity against the virus. However, with anti-viral drugs like remdesivir and practices like plasma therapy providing positive results, hope should not be lost. Concept of herd-immunity has also been discussed but that is exceedingly difficult to attain owing to the massive population.

It is indeed an extremely tough period which has caused great loss of lives and economy. On a bright note, this period has given us a chance to appreciate the great contribution of all the healthcare workers, doctors, and scientists. Unselfish devotion to their work has been instrumental in limiting the hazard caused by the virus. Hopefully with more research and information, we would be able to overcome the pandemic and restore our lives back to normal.

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