

**REVIEW ON THERAPEUTIC MANAGEMENT OF PATIENTS WITH COVID-19**

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Article Received on 29/08/2020

Article Revised on 19/09/2020

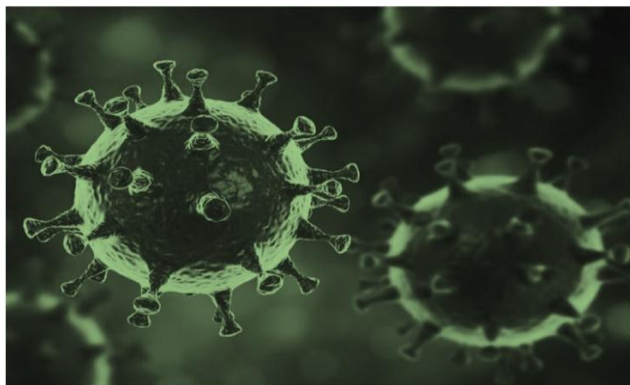
Article Accepted on 09/10/2020

**ABSTRACT**

SARS-COV-2 (severe acute respiratory syndrome corona virus) that initially came to notice in December 2019 is still spreading rapidly in whole world and it is presently a potent danger to world and also to the economy. Patients with COVID-19 are at still risk of acute respiratory distress syndrome (ARDS), respiratory failure and death. Patients aged > 60 years with comorbidities, children and health care worker are highly vulnerable to this virus patients shows various symptoms most commonly cough, fever, difficulty in breathing, fatigue, sore throat. The detailed information about the analysis of death rate by different factors like age, sex and health condition are given. Various diagnostic test for diagnosis of Covid 19 such as paper based test, RNA vaccine, molecular assay, in house develop molecular assay are discussed. General treatment can cure the disease symptomatic treatment, by using antiviral drugs, antimalarial drugs, immunomodulators, antibiotics, anti-inflammatory, vitamin D, Convalescent plasma therapy, oxygen therapy and by enhancing the immune system. Numerous clinical trials are currently under progress to test the efficacy and safety of variety of approved drugs to treat Corona virus. The review focus on latest development of diagnostic tests, vaccines, and treatment approaches for COVID-19. Here in this review all therapeutic agents against COVID-19 reported in recent times after the outbreak are being discussed.

**KEYWORDS:** Diagnosis, Antivirals, Severe Acute Respiratory Syndrome, Treatment**INTRODUCTION**

An epidemic mystical disease was observed in China specifically in Wuhan city in Hubei province at end of December 2019. The disease was presumed as pneumonia but later it was found to be novel coronavirus (CoV). It was known as 2019-nCoV which comes out to be 2019-novel CoV, which was never seen in animals or humans before.<sup>[1]</sup> The structure of covid-19 shown in Fig.1.

**Fig. 1: Structure of Coronavirus.**

Coronavirus disease 2019, which can be abbreviated as COVID-19 has now become a pandemic. It's caused

because of SARS-COV2 and it is considered to be a causative of a severely fatal disease of great public health concern. Severe acute respiratory syndrome CoV2 (SARS-CoV2) was name given to the pathogen, and the pertinent contaminated condition was termed CoV disease 2019 (COVID-19) by World Health Organization (WHO). Huanan seafood market in Wuhan city had majority of COVID-19 cases initially and then the market place was closed on 1<sup>st</sup> January 2020. On 11th March 2020 WHO World Health Organization confirmed the endemic as a pandemic.<sup>[2]</sup> Corona viruses are enveloped, giant, unsegmented positive-sense single-stranded RNA viruses with different genome size between 26-32 kb.<sup>[3]</sup> At present there are four families of coronaviruses they are alpha, beta, gamma and delta. The origin of gamma and delta from pigs, birds whereas alpha and beta are originated from bats. The four out of six species are capable of causing disease in humans. Names of four species are HKU1, OC43, 229E and NL63 they are quiet common and cause symptoms similar to that of common cold however the rest of the two are majorly responsible for (SARS-CoV), also responsible for outbreak of (SARS) in Guangdong, China 2002-2003. These also were responsible for Middle East respiratory syndrome coronaviruses (MERS-CoV). Agent that causes SARS-CoV2 can replicate in lower as well as upper respiratory tract, with

help of interaction between the angiotensin-converting enzyme II (ACE2) receptor and viral spike (S) protein. Some of extensively found common symptoms in early stages of SARS-CoV2 are dyspnea (18%), fever (88%), fatigue (38%), myalgia (14%) and cough (67%). Also other symptoms are observed like dizziness, abdominal pain, headache, sputum production, vomiting, and diarrhea also some upper respiratory tract symptom like sore throat, rhinorrhea, nasal congestion. This leads to complications such as acute kidney injury, ARDS, septic shock, arrhythmia, acute cardiac injury pneumonia and secondary infections.<sup>[4]</sup> The disease does affect much to children, even if it does only minor or no symptom infections are observed but case is just the opposite for older people as disease is extremely severe to elderly patients. The mortality rate is largely affected by the fact that whether or not the has some pre-existing medical conditions like cardiovascular diseases, diabetes, chronic respiratory diseases, and cancer are at higher risk in such cases COVID-19 despite of taking safety and sanitary measures like isolation, social distancing, quarantization, respiratory hygiene and also avoidance of public gathering it is observed that the disease contagiously passes on and multiplies at a higher rate. To cope with such a dangerous pandemic a potential and optimal therapeutic needs to be developed.<sup>[5]</sup>

### Symptoms

Greatest amount of patients suffers from common cold and flu when infected with this virus, although some may be asymptomatic. About 80% of patient will show mild symptoms are shown in about 80% of the patient with this. It is observed that adults having greatest immunity to fight against this infection but the disadvantage is they rapidly spread the infection. In 99% of patients shows fever with seriously high temperature, while remaining patients will experience fatigue, dry cough. in One-third of patient dry cough, difficulty in breathing observed. From day 1 to day 17 various symptoms of COVID-19 given below they goes from bad to worse.<sup>[6]</sup>

**Day 1:** In the first day fever together with, muscle pain, dry cough, fatigue are observed. In some patients nausea and diarrhea observed.

**Day 5:** Few Patients experienced difficulty in breathing particularly in elderly patients having earlier health condition.

**Day 7:** On the day 7<sup>th</sup> patients need to be admitted in the hospital.

**Day 8:** patients develop ARDS is develop by patients in this the fluid fills up into lungs and this is mostly fatal. Usually happens in severe cases.

**Day 10:** worsening of the symptom if the disease is in progression and at this movement the patient is shifted to ICU. Percent of death is very less.

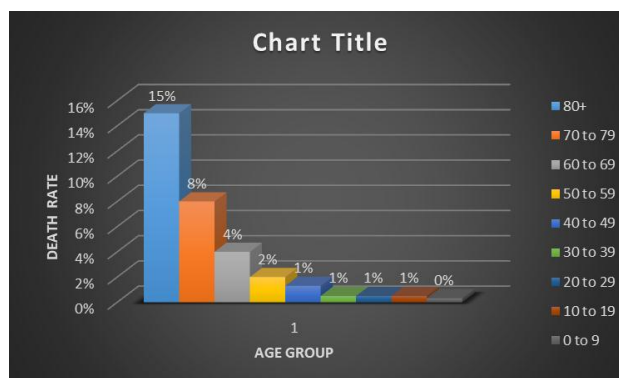
**Day 17:** After two-and-a-half weeks patients who recover are discharged from hospital. Although, it is strenuous to find out symptoms in early stages of infection. Commonly observed after 5-6 days.<sup>[7]</sup>

### Death rate due to covid-19 by various factors

The death rate is ten times highest in very elderly patients as compare with the middle-aged patients. Lower death rate in patients under 30s. In study it is observed that death rate is higher in males as compared to female.

### Death Rate by Age Group

Death Rate = Number of deaths/Number of cases = Probability of dying for those infected by the virus (%) By various research it is observed that death rate is lower in children's under 9 years and they seems to be unaffected, either with no or mild symptoms or none have died due to COVID-19 infection. Although people having above 80 years are mostly affected and those having chronic diseases. For those cross 80, approximately 14.80% of those infected dies. The death rate increase in people who have age more than 50 years. Death rate is 0.40% for those who have age below 50 years and 1.3% for those are in 50-59 years, 3.60% for people in 60-69 years range, 8% for those who are in 70-79% and 14.8% for people with age. Shown in Fig. 2.



**Fig. 2: COVID-19 death rate by different age group.**

### By Sex Ratio

In various study it is observe that the death rate due to Covid 19 is more in men as compared with the women's. The number vary with country to country. It is not confirmed by scientists but it may be a reason that men have a lot more health destructive habits like smoking, drinking as compared to women which leads to difference in death rate according to sex ratio Show fatality sex difference.

### COVID-19 death Rate due to medical Conditions

Information made by Centers for Disease Control and Prevention (CDC) and other studies shows that death rate is more in old age people and the people who do not having the good medical conditions. People with serious illness, such as diabetes, heart, lungs disease, have a greater risk. Death rate is 1% of those who have no history of medical conditions. Death rate is 10.5% for

those who suffer from cardiovascular diseases, death rate is 7.3% for those who suffer from diabetes, death rate is 6.3% for people who suffer from Chronic respiratory disease (such as asthma and chronic obstructive pulmonary disease), death rate is 6.0% for people suffering from hypertension and death rate is 5.6% for people suffering from cancer.<sup>[8]</sup>

### Diagnostic tests for covid-19

The cases of Covid-19, Curcumin, Coronavirus, Infection, Disease.-19 rapidly increase all over the world that's why rapid diagnosis is required. By diagnosis it is clear that patient is infected with Covid-19 or not. If person exposed to the virus and symptoms are observed at that time immediately he should consult to doctor. The symptoms are varies with person to person depends upon that the doctor will decide to conduct test for Covid-19. The following terms are also taken in consideration that whether the person having exposure to patient diagnosed with COVID-19, having some travel history or the person is in the area with community spread of COVID-19 within last 14 days. The tracking and diagnostic testing of Covid-19 are censorious and it is very difficult to understand epidemiology, informing case management, and to suppressing transmissions. For testing of COVID-19, doctor or health practitioner may take samples, including a sample of saliva (sputum), a nasal swab and a throat swab, to send to a lab for testing or follow the directions of your local health authority.<sup>[9]</sup>

### Paper-Based Test

A startup company spun out from MIT is now working on a paper-based test that may deliver results in less than half an hour. Early detection of covid19 is extremely useful to prevent spreading covid19. In this test a strip of paper is required that is coated with antibodies this is bind to a particular (COVID19) protein. A second antibody is attached to gold nanoparticles, and therefore the patient's sample is added to solution of these particles. Then test strip is dipped in above solution. Suppose viral protein is present in sample, it will attached to antibodies on the paper strip and also to nanoparticle-bound antibodies, and colored spot become apparent on strip in 20 minutes. At present 2 diagnostics method of Covid-19 are available. First one is that test screens patient blood samples for antibodies against the virus. The drawback is that even after symptom are seen the antibodies are undetected. The second test is for viral DNA in sputum sample. It can diagnose the virus in initial stages of infection, but they require polymerase chain reaction (PCR), to perform this method take more times (several hours) than screens patient blood test method.<sup>[10]</sup>

### RNA Vaccines

The Cambridge-based biotech company Moderna prepared an experimental vaccine to diagnose coronavirus. That speedy turnaround is because of different benefits of RNA vaccines, MIT professor of chemical engineering Daniel Anderson, says that its most

important benefit is the speed with which it can detect new sequence and utilize it to introduce a novel vaccine. Traditional vaccines includes inactivated form of viral protein which induce an immune response. Usually, these vaccines take a longer period to be produced, also they have higher risk factor for several diseases. Vaccines that have messenger RNA have an interesting alternative because they cause host cells to give rise to many copies of the proteins they encode, promoting an effective and better immune response than proteins delivered by itself. Messenger RNA can encode viral antigens, but to work, we seek out the simplest way to deliver these antigens to a particular part of the body so that they generate an immune response. It also makes sure that the vaccine causes appropriate immune stimulation to get a strong response. RNA vaccines can also be rapidly target to different viral proteins if we understand the sequence encoding of the protein. The main object to manufacturing such vaccines is that finding effectual and secure ways to deliver them the site of action. At present it has been seen that packing vaccines into special lipid nanoparticle can improve the immune response that they produce.<sup>[11]</sup>

### Molecular Assays

Currently, several assays that detect the 2019-nCoV both commercially and in-house have been prepared or under development. Some assays may spot only the new virus and a few can also spot other strains (SARS-CoV) that are genetically alike.

### In-House Developed Molecular Assays

In some cases, the groups will be ready to dispatch reagents or reagent mixers draw up in their laboratories, with or without related fees. It's highly recommended to contact scientists. The list summarized below is not exhaustive and is being updated from time to time.<sup>[12]</sup>

### Treatments

A confirmed patient of COVID 19 needs complete barest and extra treatment, ensuring capable calorie and water absorption to reduce the risk of dehydration. Water electrolyte proportion and equilibrium need to maintain along with the of Observe needed signs and oxygen congestion; protection respiratory tract free and drag oxygen in more severe cases; measuring blood count, Creative protein, urine test, and another blood biological indexes include liver and kidney function, myocardial enzyme spectrum, and coagulation function according to patient's conditions. Chest imaging should be continuously re-examined and blood gas inquiry should be carried out when required.<sup>[13]</sup>

### Symptomatic Treatment

Control measures are needed for those patients with a high fever. Antipyretic treatment should be performed in case the temperature exceeds 38.5 °C. Warm water bath and antipyretic patches are preferred as a preventive measure to lower the temperature. Common drugs involve ibuprofen orally, 5–10 mg/kg every time;

acetaminophen orally, 10– 15 mg/kg every time. Need to administer sedative arises in case the child suffers from convulsions or seizure.<sup>[14]</sup>

### Oxygen Therapy

The chances of hypoxia are increased as the virus targets the lungs squealing catheter, cloak oxygen should be immediately provided to the patient. In emergency conditions, Non-meddling or meddling automatic ventilation should be provided to the patient.

### Boosting immunity

On top of basic illness anticipation and real protection against disease is a strong immune system. People body is exceptional capable to fight off disease when the immune system is humming and people should put to get their perfect body shape This is a time to center on all the health nature people can have been invest off, Dr. Tom Moorcroft, an osteopathic doctor who specializes in infectious disease says, origin regular action and food decision that backing people's health and turn them into habits that will lead to life-long improvements in health. During this critical situation, get adequate sleep and certain fresh air and sunlight daily. People also, stop hydrated, reduce overly processed foods and generate sure to eat sufficient microelement when they can try their best with what they may catch at grocery stock right now.<sup>[15]</sup>

### Convalescent Plasma therapy

Convalescent plasma is acquired from the patients who have been recovered from COVID-19; It normally carry good concentration of antibodies that produced by the body in response to the infection. This method has been used fortunately in the past for the treatment and management of SARS-CoV, MERS-CoV, and Ebola virus, Convalescent plasma is maintained as an investigational product because it lacks approval by FDA. Convalescent plasma showed positive results in a study conducted between January–February of this year in China, where the recovered patients with high antibody titer values were selected for plasma collection.

Exchanged of 200mL plasma to 10 seriously ill patients appear in fast increase in scientific action inward 3 days of infusion in half of the patients . Another study involving the transfer of convalescent plasma was conducted, in which the plasma of five donors who recovered from COVID-19 and had high amount of IgG antibodies were given to five patients on mechanical ventilation. No significant clinical benefits were reported although the study was terminated early and was underpowered due to the lack of patients in the city. Nevertheless, this therapy suffers from several limitations, and it is also identify with the risk of transmission of other diseases.<sup>[16]</sup>

### Antiviral Drugs

Group of antiviral drugs consist of, lopinavir/ritonavir, Interferon, arbidol, ribavirin, and chloroquine phosphate

are therapeutically useful for the treatment, prevention, and diagnosis of Novel Coronavirus-convincing Pneumonia by the National Health Commission (NHC) for provisional treatment of COVID-19.

**1. IFN- $\alpha$ :** is administered in the form of vapour inhalation by application of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day. The lot of ritonavir/lopinavir is 400 mg/100 mg for person, 2 times/day.

**2. Ribavirin:** should be conduct via intravenous infusion at a lot of 500 mg for person 2 to 3 times/day in mix with IFN- $\alpha$  or lopinavir/ritonavir. Chloroquine phosphate is orally conduct at a lot of 500 mg (300 mg for chloroquine) for person, 2 times/day.<sup>[17]</sup>

**3. Arbidol:** is orally conduct at applicable of 200 mg for adults, 3 times/day. The duration of treatment is not more than 10 days.

**4. Favipiravir:** is a new drug that is under clinical trial for treating COVID-19. On February 15, 2020, China accepted it to be a effective drug for evaluate Novel Influenza. It acts by inhibiting the enzyme RNA dependent RNA polymerase. Apart from being effective for anti-influenza virus, the drug are effective for blocking the replication of flavi-, arena-, filo-, noro-, alpha-, bunya-, and another RNA viruses. Favipiravir is changed into rapid phosphoribosylated form (favipiravir-RTP) in the cells and is known as a substrate beyond viral RNA polymerase, thus prohibit RNA polymerase action. Therefore, favipiravir can accept potential antiviral activity on SARS-CoV-2, which is an RNA virus.<sup>[18]</sup>

**5. Remdesivir:** is other investigational drug under clinical trial for the analysis of COVID-19. It is a nucleoside equivalent andbroad-spectrum antiviral. Animal experiments determined that remdesivir can effectively decrease the viral capacity in the lung tissue of mice, infected with MERS-CoV, enhanced lung function, and ease therapeutic harm to lung tissue.<sup>[19]</sup>

### Antimalarial drugs

#### 1. Chloroquine

Chloroquine is an4-aminoquinolin and mainly used as a antimalarial drug. Chlorine at position 4 and [5-(diethyl amino) pentane- 2-yl] amino group at position 7. Now chloroquine arrive as a antiviral drug. Chloroquinis mainly used for lowering and preventing malaria. It also beneficial within the diagnosis of LE, autoimmune disorder, hepatic amoebiasis, and light-sensitive skin eruptions as anti-inflammatory agent. Chloroquine is effective in case of SARS-CoV-2 in vitro. When chloroquine was given orally it got widely spread into the whole body, including lungs. The EC90 value of chloroquine against SARS-CoV-2 was 6.90 Mm, showed that chloroquine blocks SARS-CoV-2 infection, With an EC50 value of 1.13  $\mu$ M and CC50 above 100  $\mu$ M. The

EC50 values for chloroquine were 23.90 and 5.47  $\mu\text{M}$ , respectively, at 24 h and 48 h against SARS-CoV-2 in another in-vitro study. The mechanism action of chloroquine is specifically not known. Chloroquine's anti-viral and anti-inflammatory properties may give effectiveness within the treatment of COVID-19 pneumonia patients. However, there is more studies are required safety and efficacy of a chloroquine drug.

## 2. Hydroxychloroquine

To prevent the chloroquine-resistant malaria, another antimalarial drug is employed that's hydroxychloroquine. Chloroquine and its derivative hydroxychloroquine have large apparent volume of distribution, as well as longer half-lives. The terminal removal of drug from the body nearly requires a year to clear. The long half-lives made such medicines active against malaria as prophylactic agents. The drug was described to own an in-vitro efficacy against SARS-CoV Clinical safety profile of these is more than chloroquine, which recommend for an elevated regular dose. From the in-vitro study of hydroxychloroquine against SARS-CoV-2 showed that potent. It was described to possess more common effect than chloroquine against SARS-CoV-2 (in-vitro), with EC50 values 0.72  $\mu\text{M}$  vs. 5.47  $\mu\text{M}$ , respectively at 48 h. The drug acts as a weak base which will increase the pH of endosomes that preventing virus fusion. In most of the cases, hydroxychloroquine was successful in removing the nasopharyngeal carriage of SARS-COV-2 in patients infected with COVID-19 in precisely 3 to 6 days. The lower dose-dependent toxicity profile of hydroxychloroquine in humans compared to chloroquine that creates possible to use at higher doses than the observed 50% effective dose (ED50). Also, the present US treatment guidelines don't recommend the utilization of chloroquine or hydroxychloroquine in hospitalized patients with COVID-19. The serious side effects are methemoglobinemia and cardiotoxicity are observed in COVID-19 patients.<sup>[20]</sup>

## Antibiotic

### 1. Azithromycin

Azithromycin is a member of macrolide antibiotics that is semisynthetic derivatives of erythromycin. It differs from erythromycin by a methyl-substituted nitrogen atom into the lactone ring. They are broad-spectrum antibiotic, which mechanism of action is protein synthesis, they reversibly bind to ribosomal 50S subunits of microorganisms. Macrolides can lower the inflammatory activities and reduce elevated cytokine creation associated with pulmonary viral infections; however, they are unclear about their exact influence on viral clearance. Drug is an effective in acute and chronic respiratory infection. Azithromycin was also used to treat Zika and Ebola viruses, and to conquer severe respiratory tract viral infection. For the clinical study require 36 COVID-19 patients, 26 patients get hydroxychloroquine, and ten were taken as control. Six patients among hydroxychloroquine treated groups got azithromycin to stop secondary bacterial infections. On the sixth day

from the start of treatment, all patients undergoing with hydroxychloroquine and azithromycin combination were clinically cured as compared to 57.1% of patients treated with hydroxychloroquine alone. This showed that azithromycin added to hydroxychloroquine was effective for virus withdrawal. It is not known if this drug is effective for treating COVID-19, and it is not FDA-approved for this use.<sup>[21]</sup>

## Anti-inflammatory

### 1. Baricitinib

Baricitinib is inhibitor of cytokine-release, an approved anti-inflammatory drug. Baricitinib is Janus kinase inhibitor used for within the treatment of autoimmune disorder. It will be effective in treatment for SARS-CoV-2 to inhibit viral entry and inflammation. Baricitinib has more affinity towards AP2-associated protein kinase 1 (AAK1), and reducing the SARS-Cov-2 endocytosis.<sup>[22]</sup> The power of combination therapy with baricitinib is critical even with it has low binding of plasma proteins and finite interaction with cytochrome p450 (CYP) enzymes and drug transporters. Also, baricitinib also paired with the direct-acting antivirals such as (lopinavir or ritonavir and remdesivir) they already employed in the COVID-19 outbreak.<sup>[23]</sup>

## Immunomodulator

### Corticosteroids

An analysis of a clinical trials showed that, because of corticosteroids occurs the chance of death by 20% in censorious ill covid-19 patients. Hydrocortisone, dexamethasone and methylprednisolone are used. Corticosteroids are commonly want to treat patients with severe infection. However, studies require corticosteroid-treated SARS and MERS patients show disrupted infection clearance and no effect on mortality. It is prescribed that glucocorticoids are getting used for a limited period of time (3–5 days), with a dosage not more than the equivalent of methylprednisolone 1–2 mg/kg/day for COVID-19 patients with severe illness, as a elevated dose can prolong the coronavirus elimination due to immune modulatory effects. WHO updated its treatment guidance to recommend that corticosteroids can be used to treat patients with severe COVID-19. Therefore, corticosteroids should not be taking regularly. Ongoing clinical studies that involving corticosteroid therapy in critically ill COVID-19 patients will help to grasp the therapy's efficacy and safety.

The preliminary results of the recovery trial require dexamethasone (6 mg given QD for 10 days) showed reduced death rate in patients receiving respiratory support. Dexamethasone decrease the death rate by one-third of patients get invasive mechanical ventilation and by one-fifth of patients receiving oxygen support without invasive mechanical ventilation. Whereas, no effects of drug was observed in patients for mild condition not requiring oxygen support. WHO also authorized the utilization of dexamethasone in severe to critical conditions only.<sup>[24]</sup>

### Vitamin D

The vitamin D supplementation for treating of COVID-19 is used to boost your immune function. The vitamin D deficiency affects the respiratory immune function that increases the chances of COVID-19 could potentially protect against COVID-19 infection. Thus improvement in immunity through better nutrition is good factor. Thus the nutrients used as vitamin D they shows a significant role in immune function.<sup>[25]</sup>

### CONCLUSION

The current pandemic of covid-19 had induce a global health crisis. The efficacy and safety of these candidate drugs mentioned in this article treatment of COVID-19 need to be implanted in randomized controlled trials before it is used as a licensed drug against COVID-19.

### ACKNOWLEDGMENTS

All the authors are equally contributed for preparation of this review article.

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