

## Review Article

### Management of SARS- CoV-2 (COVID-19) infection with special focus on Use of Hydroxychloroquine and Lopinavir/ritonavir

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#### Editor's comment -

- A. The covid-19 pandemic is the greatest challenge for the current generation of physicians, scientists and health administrators
- B. Strict use of PPE, face masks, isolation and quarantine are the most effective methods of prevention of this infection
- C. The immunomodulator hydroxychloroquine is approved for prophylactic use in asymptomatic health care workers and household contacts. It is also approved as compassionate use for treatment of active covid-19 cases in the USA
- D. Lopinavir/ritonavir and remdesivir are used in some countries, but efficacy is doubtful
- E. Treatment with convalescent plasma may be considered in emergency situations.

**Keywords:** Coronavirus; Covid-19; Hydroxychloroquine; Isolation

The SARS- CoV-2 has spread to more than 160 countries in less than 100 days and infected more than a million humans worldwide, once human transmission started in the wet meat markets of Wuhan, China. On 11 March 2020, the WHO declared this global outbreak a pandemic. With no signs of its growing trajectory stabilising and an accompanying threat of a second wave of infection, by secondary transmission from asymptomatics and presymptomatics to the uninfected and unexposed, it is estimated that a third of the seven billion people in the world are at-risk of developing SARS-CoV-2 infection.

The SARS-CoV-2 as the novel COVID-19 is formally known, belongs to the family of coronavirus closely resembling SARS- CoV-1, which was responsible for the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002-03 starting in Guangdong province of China, infecting around 8000 people and claiming around 700 lives globally.

COVID- 19, is a non segmented positive sense ssRNA virus. Originally zoonotic, it has skipped the species barrier following an animal-to-human transmission and subsequent human- to- human transmission<sup>1</sup>. The viral genome encodes four major proteins: spike, envelope, nucleocapsid and membrane proteins<sup>2</sup>. The spike proteins are responsible for facilitating the entry of virus into the target cells, via the specific ACE2 receptor found at various sites in the body. The ones involved in COVID-19 are present on the type 2 alveolar cells and the intestinal epithelial cells (villous cells)<sup>3</sup>. The envelope proteins are responsible for the positive serology.

#### Transmission

COVID-19 is transmitted by large droplets (aerosols) and contact routes (fomites)<sup>4</sup>. In order to manage the COVID-19 pandemic, the transmission of the virus has to be contained. Aerosol or droplet transmission can be prevented by following the WHO guidelines for droplet precautions. Different surfaces harbour the virus particles for varying durations extending from few hours to days. Regular disinfection of surfaces with 70% alcohol or 0.5% sodium hypochlorite, regular washing of hands with soap and water for 20 seconds and avoidance or reduced touching of face, eyes, nose is recommended for limiting the spread of the virus<sup>5</sup>. More importantly, self isolation or physical (social) distancing of individuals needs to be practiced by the general population to limit the spread and contain the infection.

Another important factor contributing to the pandemic nature of COVID-19 is its Replication of virus R0 (naught); current estimates place the value around 2.5-2.9 which is higher than that of seasonal influenza<sup>6</sup>. A value greater than 1 signifies that the infection will increase exponentially in the population. However, the R0 is a modifiable factor and is the reflection of the virus and human behaviour. R0 onboard the Diamond Princess cruise ship was 15, emphasising the importance of social distancing, improved hygiene and isolation in containing the spread of this pandemic<sup>7</sup>. Incubation period is around 4 days (2-7) and may even extend up to 14 day<sup>4</sup>.

#### Prevention

Role of facial masks at all times in community : It is essential that all persons minimize the inoculum through aerosol acquisition through a simple mouth and nostril cover with a home- made triple layer cloth face mask, which can be anything from a handkerchief, dupatta, turban or a bandana that can be easily disinfected ( washed in soap water and dried in sunlight both of which are effective virucidal agents) and worn daily when they foray into open areas away from homes (when isolation ) or national lockdown is lifted. Wearing the mask properly or even two such masks (for

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better filtration of virus - free air) at the same time may impact ease of breathing and lessen compliance of its usage due to a closer fit around the face.

In hospitals, as a HCW, thoroughly effective personal protective equipment (PPE) is required as they need to care for patients for longer hours with large viral loads. Currently in triage areas, they would require N95 masks and bio protective items such as goggles or face protection, head cover, gowns, shoe covers and nitrile gloves. Among the individuals who are tested positive for COVID-19 requiring quarantine or isolation, require a triple layered face mask to be worn at all times during their hospital stay. However, N-95 masks are to be reserved for performing aerosol inducing procedures like intubation and tracheal aspiration. HCWs involved in house-keeping functions should wear rubber boots, longer gloves and should be trained to follow certain protective behaviour which is essential to maintain their own good health as well as the well being of the society. These include regular decontamination of surfaces regularly contacted such as mobile phones, keys, pens, etc. Avoid physical examination unless it is definitely indicated. Advise patients regarding limitation to visit clinics during these times. Thorough sanitation at home, of clothes to limit the spread to the family. It is best that we are prepared to have such PPE at all times and testing as many people as possible. Donning protective gears whenever available and complete adherence to social distancing protocols is mandated.

Infection with COVID-19, typically produces no symptoms (asymptomatic) to mild symptoms like mild fever, cough and occasionally diarrhoea. The disease however may progress to potentially fatal Acute respiratory distress syndrome (ARDS) and Severe Acute Respiratory Infection (SARI). The development of ARDS follows destruction of the alveolar cells and hyaline membranes. This is secondary to the cytopathic effects of the virus and the immune response of the body. Fatality of the disease

occurs due to hyperinflammation, a response by the adaptive immunity that progresses to immunopathological dysregulated cytokine storm, macrophage blockade representing a virus induced Haemophagocytic lymphohistiocytosis and effect on coagulation cascade in the pulmonary vessels impacting oxygenation<sup>8</sup>. Besides a virus induced effect on the haemoglobin chain moiety affects the oxygen delivery to tissues and inducing other organ failure.

**Diagnosis:**

Performance of Detection Methods Over Time (Sensitivity Scores, Days Post-Symptom Onset)

Current update of Covid-19 (April 21,2020)  
**Total cases globally: 2314621**  
**Total death globally: 157847**  
**India total cases: 18601**  
**India total deaths: 590**

Table 1: gives the information regarding the various serological tests that can be performed and their sensitivity scores over the timeline of COVID-19 infection<sup>10</sup>.

SARS-CoV-2 Test	Days after Symptom Onset		
	1–7	8–14	15–39
RNA by RT-PCR	67%	54%	45%
Total Antibody	38%	90%	100%
IgM	29%	73%	94%
IgG	19%	54%	80%

The diagnosing criteria includes clinical as well as laboratory and radiological findings. Any patient following clinical suspicion must be isolated and thoroughly investigated.

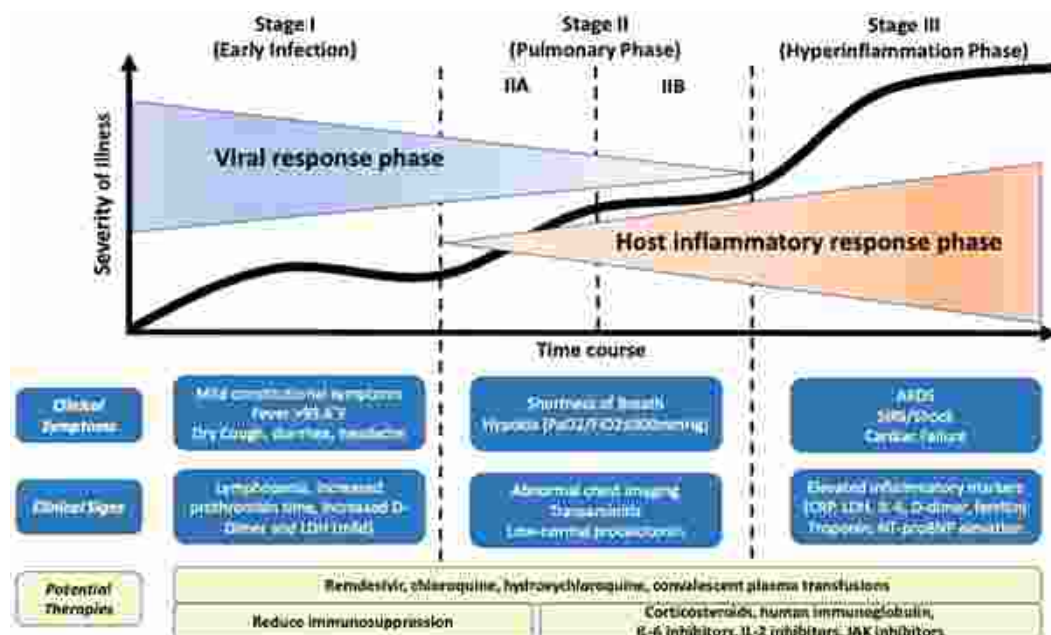


Figure 1: Covid-19: Stages, severity of illness, clinical signs, symptoms and potential therapies 9

**Table-2 : WHO Guidelines of specimens to be collected and investigations to be done for suspected individuals and contacts 11**

	Test	Type of Sample	Timing
Patient	NAAT	Lower respiratory tract <ul style="list-style-type: none"> <li>• Sputum</li> <li>• Aspirate</li> <li>• Lavage</li> </ul> Upper respiratory tract <ul style="list-style-type: none"> <li>• Nasopharyngeal</li> <li>• Oropharyngeal</li> </ul> Wash/nasopharyngeal aspirate Consider stools, whole blood, urine, and if deceased, material from autopsy	Collect on presentation. Possibly repeated sampling to monitor clearance. Further research needed to determine effectiveness and reliability of repeated sampling
Patient	Serology	Serum for serological testing once validated and available	Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 2-4 weeks later (optional timing for convalescent sample needs to be established).
Contact in healthcare centre associated outbreaks or other settings where contacts have symptoms, or where asymptomatic contacts have had high intensity contact with a COVID 19 case	NAAT	Nasopharyngeal and oropharyngeal swabs	Within incubation period of last documented contact
	Serology	Serum for serological testing once validated and available	Baselines serum taken as early as possible within incubation period of contact and convalescent serum taken 2-4 weeks after last contact (optional timing for convalescent sample needs to be established).

If possible send for Influenza virus antigens and RSV test as they have specific effective pharmacological treatment such as Oseltamivir & Ribavirin respectively. Following a diagnosis, the investigations to be done are <sup>12</sup>

- CBP with a differential count(lymphopenia suggests severe infection)
- Creatinine phosphokinase (detecting myocarditis- a significant complication)
- Baseline ECG (QTc monitoring for underlying heart diseases and management)
- Chest X-ray PA view or a CT (for various lung changes varying limited air space consolidation and diffuse interstitial pattern; and extent of lung parenchyma involvement)

**Management**

The management of COVID19 depends on clinical judgement. Adherence to the following principles reduces the risk of transmission and optimises outcome.

**Not recommended <sup>12</sup>**

- Nebulisations are to be avoided as they can result in aerosolization of the virus and increase the risk of transmission.
- Steroids both systemic and inhalational to be avoided as they can reduce immunity; however, use may be

considered for management of patients with refractory shock or acute respiratory distress syndrome. Risks and benefits must be carefully weighed.

- If the patient is on of ACE inhibitors or ARB's, these drugs should not be discontinued unless contraindicated.
- Ribavirin, a purine nucleoside analogue which prevents replication in large number of RNA and DNA viruses, earlier used in the SARS-coV epidemic is not recommended
- Avoid the use of NSAID's as there are reports of clinical deterioration in some patients following their use. For fever management Acetaminophen can be used.

**Drugs used in management**

Many drugs with antiviral and in-vitro activity against the virus are being tried in the treatment. No drug has been approved specifically for treatment.

**Hydroxychloroquine and Chloroquine:**

These are aminoquinoline compounds, used as anti-malarials, in Systemic lupus erythematosus and Rheumatoid arthritis. Currently used as off label drugs in the treatment of COVID-19 due to potential

Epidemiological- Category 1	Vital signs – category 2	Lab findings -Category 3
<ul style="list-style-type: none"> <li>• Age &gt; 55 years</li> <li>• Pre existing pulmonary disease and smoking</li> <li>• CKD</li> <li>• CAD</li> <li>• HTN</li> <li>• DM with HbA1c &gt;7.6</li> <li>• Use of biologics</li> <li>• H/o transplants</li> <li>• All HIV patients</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory rate &gt;24/min</li> <li>• Heart rate &gt;125/min</li> <li>• SPO2 &lt; 90% on room air</li> </ul>	<ul style="list-style-type: none"> <li>• Absolute lymphocyte count &lt;800 lymphocytes/microlitre</li> <li>• CRP &gt;100</li> <li>• Creatinine &gt;2 times the upper limit of normal</li> <li>• LDH &gt;245 U/l</li> <li>• Elevated troponin</li> <li>• Ferritin &gt; 300 micrograms/ l</li> <li>• D-dimer &gt;1000 ng/ml</li> </ul>

immunomodulatory and direct antiviral effects and perhaps an effect in minimizing the cleavage of the iron from the porphyrin. The world experts are divided on its use as there are no large scale RCT studies to support its use.

Hydroxychloroquine has similar pharmacokinetics as chloroquine with the drugs being well absorbed orally, large volume of distribution, and renal excretion. Hydroxychloroquine is as effective as chloroquine but is less toxic.

At cellular levels, these drugs accumulate in intercellular vesicles such as endosomes and lysosomes where they are protonated. This results in alkalisation of endosomal pH which prevents virus entry and fusion. Inhibition of the terminal glycosylation of ACE2 receptor decreases the viral binding and entry<sup>13</sup>. It also exerts immunomodulatory effect and decreases release of cytokines like interleukin-1 and tumour necrosis factor attenuating the viral cytokine storm<sup>14</sup>

In-vitro data suggests good activity of these drugs against SARS-CoV-2 with some studies suggesting higher potency and less toxicity of hydroxychloroquine compared to chloroquine<sup>15,16</sup>.

Drug concentrations based on pharmacological modelling and in-vitro drug activity suggest that hydroxychloroquine could be used as a prophylactic in prevention of SARS-CoV2 infection<sup>15</sup>. A single dose of HCQ 800 mg may provide a lung tissue concentration that is 20 times higher than the EC50 required for inhibiting Covid-19 in the lung on day 117.

Common side effects are GI upset (nausea, vomiting, and diarrhoea). This can be minimized by dividing the drug dosage or taking it with meals. Cardiac side effects are arrhythmias (QT prolongation), cardiomyopathy and sudden death. Therefore a QTc monitoring protocol has to be followed, where a QTc of > 450ms should be thoroughly evaluated<sup>18</sup>. Hematological side effects, liver toxicity and immunological side effects are also seen. Risk of retinal damage, myopathy, neuropathy, and rarely neuropsychiatric events are reported. It can cause hypoglycaemia (common in diabetics and could be severe) therefore caution is required.

Caution is required in patients with G6PD deficiency, hepatic and renal disease. It also has several drug

interactions. Caution is required when used with drugs like azithromycin (to treat atypical respiratory pathogens causing community- acquired pneumonia which prolong QT interval.

A open label randomized control study with a small sample size (n=26, with 6 lost to follow up) conducted in France, showed that with hydroxychloroquine treatment for 10 days, there was significant viral clearance in upper respiratory tract specimens in Covid-19 patients. On day 6, 70% of hydroxychloroquine-treated patients were virologically cured compared to 12.5% in the untreated control group. The effect of which was further enhanced by azithromycin<sup>19</sup>.

A multi centric study in China reports the beneficial effects of chloroquine in treating more than 100 patients with Covid-19 associated pneumonia compared to control group<sup>20</sup>. Details of the study are not elaborated so it is difficult to evaluate the efficacy.

**Recommendations:**

There is lack of robust data suggesting the use of drug for prophylaxis or treatment. However there is evidence of effectiveness from preclinical and other small studies suggesting the use of drug from China. Based on these data some of the guidelines for the use of the drug in covid-19 patients include:

The Indian ICMR guidelines recommend the usage of hydroxychloroquine as a prophylactic for usage in asymptomatic HCW involved in the care of suspected or confirmed Covid-19 patients. It is also recommended as a prophylactic for asymptomatic household contacts of Covid-19 patients.

The dosage recommendations for healthcare workers is 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals. For asymptomatic contacts the dosage is 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.<sup>21</sup>

The Ministry of Health and Family Welfare, India recommends the use of Hydroxychloroquine in patients with severe disease and requiring ICU management, in combination with Azithromycin under close medical supervision, with monitoring for side effects including QTc interval. The dosage recommendation is 400mg twice daily

on Day 1 followed by 200mg twice daily for 4 days.

USFDA guidelines states the Emergency Use Authorization (EUA) to permit the emergency offlabel, compassionate use of hydroxychloroquine sulfate to treat adults and adolescents who weigh 50 kg or more, who are hospitalized with Covid-19 and for whom a clinical trial is not available or participation is not feasible. The dosage recommendation is 1000 mg of hydroxychloroquine sulfate on the Day 1 followed by 500 mg daily for four to seven days of total treatment based on clinical evaluation.<sup>22</sup>

In an era where it may take 12-18 months for an effective vaccine to develop; HCQ offers a practical, cheap, safe and effective agent for prevention of potentially lethal COVID19 infection.

### **LOPINAVIR/RITONAVIR**

Lopinavir and ritonavir are protease inhibitors approved for the treatment of HIV. Ritonavir boosted lopinavir is used to reduce the dose of lopinavir and increase the plasma levels through CYP3A isoenzyme inhibition. This regimen is used as a second line drug in the treatment of HIV and also in post exposure prophylaxis<sup>23</sup>.

Lopinavir is a potent inhibitor of protease Mpro, blocking the cleavage of nascent viral proteins and thus inhibiting coronavirus replication and activity. Among the HIV protease inhibitors, lopinavir has shown highest activity against CoV22,<sup>23</sup>. In vitro studies and preclinical studies on animals has shown good activity of these drugs for coronaviruses (SARS-CoV and MERS-CoV)<sup>26,27</sup>

A similar study, patients with SARS were treated with a combination of lopinavir/ritonavir and ribavirin showed better clinical outcomes and decreased viral load when compared to historical matched controls treated with ribavirin only.<sup>28</sup>

A recently conducted randomized control trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19 (n=199) in China showed that treatment with lopinavir-ritonavir for 14 days was not associated with any significant benefit in comparison to the standard care in time to clinical improvement, mortality or viral RNA titres.<sup>29</sup>

A retrospective cohort study of hospitalized Covid-19 patients in China reviewed the clinical course and risk factors for mortality, included 29 patients who received lopinavir-ritonavir. They found no difference in viral shedding after treatment with lopinavir-ritonavir<sup>30</sup>

### **Dosage**

Lopinavir/ritonavir is given in a dosage of 200 mg/50 mg - two tablets twice daily for 14 days or for seven days after the patient becomes asymptomatic, whichever is earlier, or as 400/100 mg twice daily for 10 days.

### **Side effects**

The side effects with these drugs are gastrointestinal side effects like nausea, vomiting, diarrhea, dysgeusia and abdominal pain. Hypercholesterolemia, increased serum triglycerides, redistribution of fat and hyperglycaemia are seen. Rashes, fatigue, weakness, and hypersensitivity reactions are reported. Rare but severe side effects are

pancreatitis, QT prolongation, increased risk of myocardial infarction and, hepatotoxicity. The drug has significant drug -interactions and care should be taken when combining it with other drugs like azithromycin and chloroquine.

### **Recommendations:**

In view of the efficacy data from in-vitro studies, clinical trials and studies, the Indian Council of Medical Research (ICMR)/CDSCO has suggested off-label emergency use of lopinavir/ritonavir for restricted use in symptomatic Covid-19 patients in India and a trial evaluating its safety and efficacy is underway<sup>31</sup>. Outcomes from this trial will further help in planning of guidelines for our country. FDA has not approved this drug combination for use in Covid-19 patients. This drug combination is evaluated as a part of WHO SOLIDARITY trial.

### **Remdesivir (RDV)**

This is a broad spectrum antiviral agent; a nucleotide analogue with in-vitro activity against corona virus<sup>32</sup>. It is not available commercially. It was first tried on quarantined patients of Diamond Princess Cruise ship at the University of Nebraska medical centre and positive results were seen. Remdesivir has been administered to patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan through Expanded Access or Compassionate Use programs. The current dose RDV 200 mg IV loading followed by 100 mg IV daily for 10 days<sup>12</sup>

### **Tocilizumab**

Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody Tocilizumab, may ameliorate severe damage to the lung tissue caused by the cytokine release and is given to patients with evidence of cytokine release syndrome. A retrospective review analyzed the effect of tocilizumab, added to standard therapy in COVID-19 patients and preliminary data suggests clinical benefit of tocilizumab as adjunctive therapy<sup>33</sup>.

### **Convalescent plasma**

Plasma from persons who have recovered from COVID-19 infection may contain antibodies to SARS-CoV-2. The possible mechanisms suggesting efficacy of convalescent plasma studies in various respiratory infections is that the antibodies from convalescent plasma might suppress viraemia<sup>34</sup>. ICMR has suggested the use of convalescent plasma to treat patients with severe or life-threatening COVID-19 infections.

### **Other drugs include;**

#### **Azithromycin:**

This is a macrolide antibacterial which has immunomodulatory properties in pulmonary inflammatory conditions. In a small open label study of HCQ in France; azithromycin was given to prevent potential bacterial superinfection. Lower viral loads were seen in the patients but the results did not vary much with those receiving Hydroxychloroquine alone<sup>19</sup>.

#### **Ivermectin**

Studies conducted at Monash University have found the efficacy of Ivermectin, an anti-helminth having broad

spectrum anti viral properties in vitro, in inhibiting the replication of covid19 in -vitro within 48 hours; however these studies have been performed in vitro and determination of its action and appropriate dosage in humans is yet to be determined<sup>35</sup>.

Many others drugs with antiviral activity are being tried in few studies like Ascorbic acid , Inhalational Nitric oxide, Zinc etc. These compounds do not have much clinical evidence and care should be taken in prescribing them to patients.

### Conclusion

COVID-19 has caused a pandemic and has become a pressing issue for physicians around the globe; attention to it is happening at the cost of other ailments which require regular intervention such as dialysis for CKD patients, ART for HIV patients and chemotherapy for cancer patients. Any negligence on this front might result in co- morbidities and fatalities occurring during and after the COVID-19 pandemic. There are several treatment options underway and with the resilience of governments and medical staff around the globe, this pandemic will run its course soon. However, the chances of it prevailing as an endemic disease and resulting in occasional outbreaks is a real long-term threat.

A concept of behavioural distancing where man distances himself from encroaching and exploiting the habitats of the wild offers hope to prevent similar zoonotic pandemics. Another matter of concern is how this pandemic and its consequences have taken a toll on the mental well being of the general population and health care workers alike. Stigmatisation and discrimination are further add-ons to this stress. Identification and minimisation of such is a matter of concern not only for the physicians but also the governments.

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