

# Review of the Available Treatment for COVID-19

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**Abstract:** *In the late 2019, a novel corona virus appeared as outbreak of acute respiratory illness in wuhan, a city in china. Causative virus for the illness is known as SARS corona virus 2. The name given to the illness by WHO is COVID-19. (CORONA VIRUS DISEASE 2019). WHO designated it as public health emergency as it caused respiratory illness worldwide among multiple countries. It should be suspected in the patients with fever and/or respiratory track symptoms. It has a incubation period of 2-14 days (median 4-5days). It can cause mild pneumonia in about 80% cases, severe infection in about 14% cases. Among those 14% cases, 5 % can develop critical illness like acute respiratory failure, shock, multiple organ dysfunction syndrome. Case fatality rate is variable among countries. It seems 2-3% among most of countries. It presents as variable symptoms like fever (90%), fatigue (70%), dry cough (60%), anorexia (40%), productive cough (30%), ARDS (20%), headache, sore throat, nausea, vomiting, muscle ache, diarrhea. Recently, it comes into the notice in clinicians who are treating COVID-19, this virus cannot cause ARDS. It displaces oxygen and displace iron. This free iron can cause inflammation of alveolar wall and leads to changes in respiratory track. Some researcher says it's more like chemical pneumonia rather than viral pneumonia. These viruses attaches beta chain and dissociates heme, removing iron and convert it to porphyrin. Virus can dissociate oxy-Hb, carboxy-Hb and glycosylated Hb. That's why it seems bad in diabetics. The higher HbF and HbA2 prevent children from having disease. Fatality in COVID-19 is believed to be due to cytokine storm syndrome (which can cause MODS) and fulminant myocarditis. RTPCR is confirmatory test but sensitivity of swab collected from different site is variable. oropharynx has lowest one with BAL has the highest one. HRCT has key role in diagnosing disease earlier. Comorbidities like Hypertension, Diabetes, Obesity, persistent positive swab and rising transaminases are poor prognostic factor. Various treatments have been tried in multiple clinical trials but no drug has been approved by FDA yet. FDA just released statement on compassionate use of hydroxychloroquin. Here we discuss multiple trials about use of drugs in COVID-19.*

**Keywords:** COVID-19, Treatment, Trials, Coronavirus, Pandemic, hydroxychloroquine, SARS-CoV

## 1. Introduction

### Hydroxychloroquin

Chloroquine has been used in treating SARS-CoV-2 virus. Hydroxychloroquine has the same mechanism of action as chloroquine. HCQ has more tolerable safety profile, so its preferred drug to treat malaria and SLE, RA, SJOGRENS. Immunomodulatory effect of hydroxychloroquine also may be useful in controlling the cytokine storm that occurs late-phase in critically ill COVID 19 patients. There is no evidence available to support the use of hydroxychloroquine in SARS-CoV-2 infection.<sup>1</sup>Hydroxychloroquine was found to be more potent than chloroquine in vitro. In PBPK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance.<sup>2</sup>French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16<sup>th</sup>, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more

efficient for virus elimination. <sup>3</sup>Chloroquine / hydroxychloroquine at correct dose may be a valuable to be used in low-cost antiretroviral combinations. Participants should be regularly monitored to prevent retinopathy. According to new in-vitro results, the antiretroviral effects of chloroquine are attributable to the inhibition of viral particle glycosylation. These effects appeared to be specific, since the chloroquine concentrations effective in vitro neither affected any other step in HIV-1 replication nor were cytotoxic. Chloroquine might inhibit replication of the SARS coronavirus has been confirmed in two independent in-vitro studies.

- 1) Belgian Catholic University of Leuven found that chloroquine inhibited SARS coronavirus replication with a 50% effective concentration of 8.8 (SE 1.2)  $\mu\text{mol/L}$ , within the range of blood concentrations achievable during antimalarial treatment. The dose inducing 50% cytostatic activity was much higher (261.3 [14.5]  $\mu\text{mol/L}$ ). Time-of-addition experiments indicated that chloroquine affected an early stage of SARS coronavirus replication.
- 2) Centers for Disease Control and Prevention (Atlanta, GA, USA) reported potent anti-SARS coronavirus effects of chloroquine in vitro, attributable to a deficit in the glycosylation of the SARS coronavirus receptor ACE2. Again, the antiviral drug concentrations were not cytotoxic. If animal models confirm these results, chloroquine might represent a valuable therapeutic option if SARS re-emerges.

The broad spectrum antiviral effects of chloroquine deserve particular attention in a time in which the world is threatened

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by the possibility of a new influenza pandemic, and the availability of effective drugs would be fundamental during evaluation of an effective vaccine. The effect of chloroquine against replication of Orthomyxoviridae has long been known. Inhibitory effects of chloroquine on both type A and B influenza viruses have been described. Glycosylation inhibition might represent a major mechanism for the antiviral effects of chloroquine, suggesting that specific interactions of chloroquine with sugar-modifying enzymes or glycosyltransferases may occur within human cells. Chloroquine was recently shown to inhibit quinone reductase 2, a structural neighbour of UDP-N-acetylglucosamine 2-epimerases, which are involved in sialic acid biosynthesis. If chloroquine should indeed inhibit the biosynthesis of sialic acid, this effect could explain not only the effects of chloroquine on HIV and SARS coronavirus (sialic acid moieties are present in HIV-1 glycoproteins and SARS coronavirus receptor ACE2), but also the in-vitro effects on orthomyxoviruses (which use sialic acid moieties as receptors). These effects deserve further investigation, in that they may lead to new strategies controlling the replication of several viruses.<sup>4</sup>

### The Marseille Study

In addition, comparing untreated patients, those receiving hydroxychloroquine and those given hydroxychloroquine plus the antibiotic azithromycin, the results showed there was "a spectacular reduction in the number of positive cases" with the combination therapy, said Prof Raoult. At 6 days, among patients given combination therapy, the percentage of cases still carrying SARS-CoV-2 was no more than 5%.<sup>5</sup> Hydroxychloroquine and chloroquine are oral prescription drugs that have been used for treatment of malaria and certain inflammatory conditions. Chloroquine has been used for malaria treatment and chemoprophylaxis, and hydroxychloroquine is used for treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda. Both drugs have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2.<sup>10</sup> The transition from first symptoms to acute respiratory distress syndrome (ARDS) is highly likely to be due to uncontrolled cytokine release. There is an urgent need to identify safe and effective drugs for treatment. Chloroquine (CQ) exhibits a promising inhibitory effect. However, the clinical use of CQ can cause severe side effects. We propose that hydroxychloroquine (HCQ), which exhibits an antiviral effect highly similar to that of CQ, could serve as a better therapeutic approach. HCQ is likely to attenuate the severe progression of COVID-19, inhibiting the cytokine storm by suppressing T cell activation. It has a safer clinical profile and is suitable for those who are pregnant. It is cheaper and more readily available.<sup>17</sup> One study showed that chloroquine could reduce the length of hospital stay and improve the evolution of COVID-19 pneumonia, leading to recommend the administration of 500 mg of chloroquine twice a day in patients with mild, moderate and severe forms of COVID-19 pneumonia. For us, the activity of hydroxychloroquine on viruses is probably the same as that of chloroquine since the mechanism of action of these two molecules is identical, and we are used to prescribe for long periods hydroxychloroquine, which would be therefore

our first choice in the treatment of SARS-CoV-2. For optimal treatment, it may be necessary to administer a loading dose followed by a maintenance dose.<sup>18</sup> Chloroquine acts by increasing the pH of intracellular vacuoles and altering protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational protein modification in the Golgi apparatus. In macrophages and other antigen-presenting cells, chloroquine interferes with the antigen processing, thereby achieving an antirheumatic response. Studies have demonstrated that chloroquine also confers its considerable broad-spectrum antiviral effects via interfering with the fusion process of these viruses by decreasing the pH. Additionally, it alters the glycosylation of the cellular receptors of coronaviruses. Hydroxychloroquine, a less toxic aminoquinoline, has an N-hydroxy-ethyl side chain in place of the N-diethyl group of chloroquine. In addition, hydroxychloroquine has a modulating effect on activated immune cells, downregulates the expression of Toll-like receptors (TLRs) and TLR-mediated signal transduction, and decreases the production of interleukin-6. Although the antimalarial activity of hydroxychloroquine is equivalent to that of chloroquine, hydroxychloroquine is preferred over chloroquine for its lower ocular toxicity. Retinopathy is a dose-limiting adverse effect of hydroxychloroquine, but a safe daily dose seems to correspond to 6.5 mg/kg of the ideal body weight and 5.0 mg/kg of the actual body weight. Although there are more clinical data about chloroquine's anti-coronaviral activity than those about hydroxychloroquine's, both these agents are theoretically similar in their antiviral activity. In addition, chloroquine is associated with greater adverse effects than hydroxychloroquine. For example, in patients with COVID-19, chloroquine can interact with lopinavir/ritonavir, resulting in prolongation of the QT interval. Hence, it is necessary to consider hydroxychloroquine instead of chloroquine when the latter is not available for treating patients with COVID-19.<sup>19</sup>

Prophylaxis Dose: 200mg 3 times daily for 10 days (GAUTRET 2020) OR  
400mg bd on day 1 followed by 200mg bd for 4 days (CDC 2020, YAO 2020) OR  
400mg bd on day 1 followed by 400mg od for 5 days OR  
600mg bd on day 1 followed by 400mg od for 4 days (CDC 2020) OR  
400mg bd on day 1 followed by 400mg once a week for next 7 week to be taken with meal for healthcare worker/ for 3 week for household contact (ICMR)

### Lopinavir and Ritonavir

In view of the earlier evidence about effectiveness of repurposed lopinavir/ritonavir against severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus (CoV), multiple studies have been conducted. Forty one patients with SARS followed for 3 weeks were treated with a combination of lopinavir/ritonavir and ribavirin. The clinical progress and virological outcomes were monitored and compared with 111 patients treated with ribavirin only who served as historical controls. The adverse outcome remained significantly lower in the treatment group than in the controls-both those diagnosed early ( $p < 0.001$ ) and those diagnosed later in the course of the epidemic ( $p = 0.002$ )-but

there was no significant difference in adverse outcome rates between the two time periods ( $p = 0.548$ ). No time related difference in outcome was observed in the control groups. A reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir, and these patients had a decreasing viral load and rising peripheral lymphocyte count. Multivariate analysis showed that age, hepatitis B carrier status, and lack of treatment with this antiviral combination were independent predictors of an adverse outcome. Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level.<sup>6</sup>In conclusion, we found that lopinavir–ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious Covid-19. These early data should inform future studies to assess this and other medication in the treatment of infection with SARS-CoV-2. Whether combining lopinavir–ritonavir with other antiviral agents, as has been done in SARS and is being studied in MERS-CoV, might enhance antiviral effects and improve clinical outcomes remains to be determined. This swiftly performed, well-executed study shows mortality was somewhat lower with this medication, the effect was neither striking nor significant. Despite these results, the WHO is launching a large study that includes lopinavir-ritonavir in one of the arms. However, based on the structure of the SARS-CoV-2 protease, many experts in the field think HIV protease inhibitors are unlikely to be active.<sup>8</sup> lopinavir/ Ritonavir (400/100 mg) twice daily dose can be used for two days.<sup>7</sup>

### REMEDESIVIR

In late January 2020, in response to the 2019–20 coronavirus pandemic, Gilead began laboratory testing of remdesivir against SARS-CoV-2, stating that remdesivir had been shown to be active against SARS and MERS in animal models of CoV infection. It also provided remdesivir for treatment of a "small number of patients" in collaboration with Chinese medical authorities. Also in late January 2020, remdesivir was administered to the first U.S. patient confirmed to be infected by SARS-CoV-2, in Snohomish County, Washington, for "compassionate use" after he progressed to pneumonia. While no broad conclusions can be made based on the single treatment, the patient's condition improved dramatically the next day, and he was eventually discharged. Also in late January 2020, Chinese medical researchers reported that remdesivir and two other drugs, hydroxychloroquine and favipiravir, seemed to have "fairly good inhibitory effects" on SARS-CoV-2 (after exploratory research that examined 30 drug candidates), after which requests to begin clinical testing were submitted. On 6 February 2020, a clinical trial of remdesivir began in China. On 17 March 2020, remdesivir was provisionally approved for use for COVID-19 patients in a serious condition in the Czech Republic. While no broad conclusions can be made based on the single treatment, results of remdesivir treatment of an Italian COVID-19 patient in Genoa, a 79-year-old, were described as successful on 18 March 2020. Other patients also received the treatment, the results of which are not known. On that date, the WHO announced the launch of a large four-arm pragmatic clinical trial (SOLIDARITY trial) that includes one group of patients treated with remdesivir. It was

announced that Cleveland, Ohio-based University Hospitals would run two clinical trials to test the effectiveness of remdesivir against coronavirus. On the same date, President Trump announced that remdesivir was now available for "compassionate use" by patients that had tested positive for COVID-19; FDA Commissioner Stephen Hahn confirmed the statement at the same press conference. That decision allowed physicians of COVID-19 patients to request permission to use the unapproved drug in the context of remdesivir's investigational new drug (IND) status, outside of participation in a formal clinical trial, Gilead suspended access to remdesivir for compassionate use (excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide agent for testing in clinical trials.<sup>9</sup>

Remdesivir 200mg od on day 1 followed by 100mg od for duration of 5 to 10 days.<sup>13</sup>

### Surgical Mask VS N95 Mask

Surgical mask is a loose-fitting, disposable device that creates a physical barrier between the mouth and nose of the wearer and potential contaminants in the immediate environment. Surgical masks are made in different thicknesses and with different ability to protect you from contact with liquids. These properties may also affect how easily you can breathe through the face mask and how well the surgical mask protects you. If worn properly, a surgical mask is meant to help block large-particle droplets, splashes, sprays, or splatter that may contain germs (viruses and bacteria), keeping it from reaching your mouth and nose. Surgical masks may also help reduce exposure of your saliva and respiratory secretions to others. It does not filter or block very small particles in the air that may be transmitted by coughs, sneezes, or certain medical procedures. Surgical masks also do not provide complete protection from germs and other contaminants because of the loose fit between the surface of the face mask and your face.<sup>11</sup> The standard surgical mask (left), also known as a fluid-resistant surgical mask (FRSM). If worn by the caregiver, the surgical mask protects the patient and his or her environment (air, surfaces, equipment, surgical site). If worn by a contagious patient, it prevents the patient from contaminating his or her surroundings and environment.<sup>12</sup>

These points to note before using surgical mask

- 1) Surgical masks are not to be shared and may be labeled as surgical, isolation, dental, or medical procedure masks. They may come with or without a face shield. These are often referred to as face masks, although not all face masks are regulated as surgical masks.
- 2) Surgical masks are not intended to be used more than once.
- 3) If your mask is damaged or soiled, or if breathing through the mask becomes difficult, you should remove the face mask, discard it safely, and replace it with a new one.
- 4) To safely discard your mask, place it in a plastic bag and put it in the trash.
- 5) Wash your hands after handling the used mask.
- 6) They should be changed when they become moistened or damaged, and should not be undone and dangled round the neck between procedures.

- 7) It should be worn with eye protection
- 8) These masks should not be worn for more than 3 to 8 hours.

### N95 Respirators

The respirator mask, available in the USA as N95 mask and in the UK as an equivalent FFP ('filtering face piece') mask, is used to prevent the user from inhaling small airborne particles in aerosol-generating procedures (AGPs). It must fit tightly to the user's face. There are three categories: FFP1, FFP2 and FFP3. FFP3 provides the highest level of protection. Again, this mask must be worn with eye protection.<sup>12</sup> An N95 respirator is a respiratory protective device designed to achieve a very close facial fit and very efficient filtration of airborne particles. The 'N95' designation means that when subjected to careful testing, the respirator blocks at least 95 percent of very small (0.3 micron) test particles. If properly fitted, the filtration capabilities of N95 respirators exceed those of face masks. However, even a properly fitted N95 respirator does not completely eliminate the risk of illness or death. N95 respirators are not designed for children or people with facial hair. Because a proper fit cannot be achieved on children and people with facial hair, the N95 respirator may not provide full protection.<sup>11</sup> Respirators are divided into two categories: insulating and filtering. Filtering respirators consist of a facepiece and a filtering device. Sometimes the filter element is integrated into the facepiece. Depending on the type of filter, the mask will either be effective only against particles, only against certain gases and vapors, or against particles, gases and vapors. Filtering respirators can sometimes also be equipped with an exhalation valve to improve user comfort. The valve prevents condensation inside the mask, misting on the glasses and helps the user breathe in and out easily.

In Europe, they must meet the European standard EN 149: 2001 which has three classes of disposable particulate respirators (FFP1, FFP2 and FFP3).

- FFP1 refers to the least filtering of the three masks with an aerosol filtration of at least 80% and leakage to the inside of maximum 22%. This mask is mainly used as a dust mask (home renovations and various types of work).
- FFP2 masks have a minimum of 94% filtration percentage and maximum 8% leakage to the inside. They are mainly used in construction, agriculture, and by healthcare professionals against influenza viruses. They are currently used for protection against the coronavirus.
- FFP3 masks are the most filtering mask of the FFPs. With a minimum filtration percentage of 99% and maximum 2% leakage to the inside, they protect against very fine particles such as asbestos.

In the United States, respirators must meet NIOSH (National Institute for Occupational Safety and Health) standards. Within this standard, there are several classes of respirators depending on the degree of oil resistance:

- Class N: no oil resistance. A distinction is made between N95, N99 and N100. The number after the letter indicates the percentage of filtration of suspended particles.
- Class R: mask resistant to oil for up to eight hours. Here again, a distinction is made between R95, R99 and R100.

- Class P: a completely oil-resistant mask. There are also P95, P99 and P100.

### Azithromycin

To evaluate if early administration of azithromycin, started prior to the onset of severe LRTI symptoms, in preschool children with recurrent severe LRTIs can prevent the progression of these episodes. Among young children with histories of recurrent severe LRTIs, the use of azithromycin early during an apparent RTI compared with placebo reduced the likelihood of severe LRTI. More information is needed on the development of antibiotic-resistant pathogens with this strategy.<sup>14</sup> Hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients. A significant difference was observed between hydroxychloroquine-treated patients and controls starting even on day3 post-inclusion. These results are of great importance because a recent paper has shown that the mean duration of viral shedding in patients suffering from COVID19 in China was 20 days (even 37 days for the longest duration). Very recently, a Chinese team published results of a study demonstrating that chloroquine and hydroxychloroquine inhibit SARS-CoV-2 in vitro with hydroxychloroquine (EC50=0.72% $\mu$ M) found to be more potent than chloroquine (EC50=5.47% $\mu$ M). These in vitro results corroborate our clinical results. The target values indicated in this paper were reached in our experiments. The safer dose-dependent toxicity profile of hydroxychloroquine in humans, compared to that of chloroquine allows using clinical doses of hydroxychloroquine that will be over its EC50 observed in vitro<sup>14</sup>. Our preliminary results also suggest a synergistic effect of the combination of hydroxychloroquine and azithromycin. Azithromycin has been shown to be active in vitro against Zika and Ebola viruses and to prevent severe respiratory tract infections when administrated to patients suffering viral infection. This finding should be further explored to know whether a combination is more effective especially in severe cases. potential risk of severe QT prolongation induced by the association of the two drugs has not been established yet but should be considered. As for each treatment, the cost benefits of the risk should be evaluated individually. Further studies on this combination are needed, since such combination may both act as an antiviral therapy against SARS-CoV-2 and prevent bacterial super-infections. The cause of failure for hydroxychloroquine treatment should be investigated by testing the isolated SARS-CoV-2 strains of the non-respondents and analyzing their genome, and by analyzing the host factors that may be associated with the metabolism of hydroxychloroquine. Therefore It is recommended that COVID-19 patients be treated with hydroxychloroquine and azithromycin to cure their infection and to limit the transmission of the virus to other people in order to curb the spread of COVID-19 in the world. Further works are also warranted to determine if these compounds could be useful as chemoprophylaxis to prevent the transmission of the virus as this study had lower sample size.<sup>15</sup> Macrolide reduce the mortality by treating superadded infection in viral pneumonia<sup>16</sup> Macrolides have been reported to be associated with improved outcomes in patients with viral pneumonia related to influenza and other viruses, possibly because of their immune-modulatory

effects. Macrolides have frequently been used in patients with Middle East Respiratory Syndrome (MERS). This study investigated the association of macrolides with 90-day mortality and MERS coronavirus (CoV) RNA clearance in critically ill patients with MERS. The findings indicate that macrolide therapy is not associated with a reduction in 90-day mortality or improvement in MERS-CoV RNA clearance<sup>20</sup>

### Osetamivir

According to WHO, Osetamivir should be used before or after exposure to pandemic influenza.<sup>21</sup> Human cells have sialic acid containing glycoprotein which is cleaved by enzyme neuraminidase. Osetamivir inhibits enzyme neuraminidase. Thus, osetamivir prevents release of new virions from host cell. Hence, reducing further respiratory tract involvement.<sup>22</sup> Effectiveness of osetamivir, is not yet proved in treatment of COVID-19.<sup>23</sup> However, around the world many doctors are using it in COVID19 patients and astonishingly few cases have shown reduction in virus production.<sup>24</sup> A clinical trial of osetamivir with combination treatment of various protease inhibitors on 80 patients is in its phase 3.<sup>25</sup>

### Aviptadil

Aviptadil is a drug used for treating erectile dysfunction along with phentolamine where it was associated with high discontinuation rates and moderate side effect profile<sup>26</sup>. It has also been used in treating pulmonary hypertension. Nonclinical studies demonstrate that VIP is highly concentrated in the lung where it prevents NMDA-induced caspase-3 activation in the lung and also inhibits IL6 and TNF alpha production and protects against HCl-induced pulmonary edema. Aviptadil restores barrier function at the endothelial/alveolar interface and thereby protects the lung and other organs from failure. Currently a study is underway, done by NeuroRx, incorporated, which is studying effects of aviptadil on patients with ARDS due to COVID 19 infection. The results are expected to arrive at august 2020.

### Darunavir

Unsubstantiated reports claim that darunavir has an antiviral effect against COVID-19. Johnson & Johnson, the drug proprietor, has no evidence that darunavir has any effect against SARS-CoV-2, the virus that causes COVID-19. Darunavir, is in the process of being evaluated in-vitro for potential antiviral activity against SARS-CoV-2. The in-vitro antiviral activity of DRV against SARS-CoV-2 was assessed. DRV showed no activity against SARS-CoV-2 at clinically relevant concentrations (EC50 >100 µM). These data do not support the use of DRV for treatment of COVID-19. Data will be published soon by Janssen, the marketer of darunavir<sup>27</sup>.

### Arbidol

Arbidol interacts and modifies the physicochemical properties of the phospholipids in the membrane, having a significant effect on negatively charged phospholipids but a minor one on zwitterionic phospholipids. The data suggest that Arbidol is located at the interface of the membrane, participates in hydrogen bonding either with water or the phospholipid or both, and decreases the hydrogen bonding

network of the phospholipids giving place to a phospholipid phase similar to the dehydrated solid one. The significant effects produced on negatively charged phospholipids suggest that the active molecule of Arbidol in the membrane is the protonated one, that is, the positively charged molecule<sup>28</sup>. The research analyzed 16 patients who received oral arbidol and LPV/r in the combination group and 17 who oral LPV/r only in the monotherapy group, and both initiated after diagnosis. Baseline clinical, laboratory, and chest CT characteristics were similar between groups. The SARS-CoV-2 could not be detected for 12 of 16 patients' nasopharyngeal specimens in the combination group after seven days, compared with 6 of 17 in the monotherapy group. After 14 days, 15 of 16 and 9 of 17, respectively, SARS-CoV-2 could not be detected. The chest CT scans were improving for 11 of 16 patients in the combination group after seven days, compared with 5 of 17 in the monotherapy group.<sup>29</sup>

### Mesenchymal cell therapy

Mesenchymal stem cells (MSCs), first described in 1968 by Friedenstein and colleagues, have been shown to reduce dysregulated inflammatory responses, to improve alveolar fluid clearance and to maintain lung epithelial and endothelial integrity in the lung during pulmonary inflammation. Much of these effects have been attributed to the secretion of growth factors, cytokines and lipid mediators. MSC-based prophylactic and treatment strategies have yielded significant therapeutic benefits in preclinical models of a variety of inflammatory diseases, including rheumatoid arthritis, sepsis and ALI. Because inflammatory ALI/ARDS is a major determinant of morbidity and mortality in severe influenza, MSC therapy represents a promising adjunctive immunomodulatory strategy to improve outcome in severe influenza<sup>30</sup>. MSCs played the vital immune modulation roles to reverse the lymphocyte subsets mainly through dendritic cells. Our previous study showed that co-culture with MSCs could decrease the differentiation of cDC from human CD34+ cells, while increasing the differentiation of pDC through PGE2. Furthermore, the induction of IL-10-dependent regulatory dendritic cells and IRF8-controlled regulatory dendritic cells from HSC were also reported in rats. MSCs could also induce mature dendritic cells into a novel Jagged-2-dependent regulatory dendritic cell population. All these interactions with different dendritic cells led to a shift of the immune system from Th1 toward Th2 responses<sup>31</sup>. The administration of intravenous injection of MSCs significantly improved the inflammation situation in severe COVID-19 patients. Due to its unique immunosuppression capacity, the serum levels of pro-inflammatory cytokines and chemokines were reduced dramatically which attracted less mononuclear/macrophages to fragile lungs, while induced more regulatory dendritic cells to the inflammatory tissue niche. Moreover, the increased IL-10 and VEGF promoted the lung's repair. Ultimately, the patients with severe COVID-19 pneumonia survived the worst condition and recovery<sup>32</sup>.

### Anti TNF therapy

Researchers have explored the use of therapeutic agents to lower host inflammation by directly targeting specific cytokines. TNF-neutralizing monoclonal antibodies and

soluble TNF-receptor fusion proteins are important in managing inflammation caused by immune-mediated disorders, such as inflammatory bowel disease and rheumatoid arthritis, and increasing survival of lipopolysaccharide (LPS) injected mice. In contrast, anti-TNF strategies have not been beneficial in the treatment of other inflammatory conditions such as sepsis. Few studies have reported that TNF neutralizing strategies for severe influenza in mouse models reduce lung lesion severity, pulmonary inflammatory cell infiltrates and T-cell cytokine production; however, with no survival benefit reported. It was seen that TNFR1  $\alpha$  mice survived longer than wild-type mice when infected with reconstructed 1918 influenza virus, suggesting that anti-TNF therapy might provide some therapeutic benefit in severe influenza, even though all mice died in both groups. Anti-TNF therapy for severe influenza in humans has not been studied in a controlled clinical trial, and its failure for the treatment of sepsis casts doubt on its potential benefit in severe clinical influenza. Additionally, increased risk of bacterial infection and infections with rare intracellular pathogens are well-described complications of anti-TNF therapy in the treatment of rheumatoid arthritis. Thus, overall experimental evidence to support the clinical use of anti-TNF therapy for severe influenza is currently lacking, especially when considering the attendant risks.

#### Sarilumab

Sarilumab is a human antibody that decreases the production of interleukin-6 (IL-6), which has been observed in cases of pneumonia in some COVID-19 patients. Cytokines are small proteins that are released in cell signaling and mediate immunity, inflammation, and other cellular responses. Pneumonia may occur due to overproduction of these cytokines. There has been previous data from China that shows the efficacy of IL-6, however, that was obtained through a non-controlled trial. The Feinstein Institutes for Medical Research is conducting the first ever controlled trial of approximately 400 severe or critical patients being hospitalized.<sup>33</sup>

#### Tocilizumab

The patients diagnosed as severe or critical in a hospital in China were given Tocilizumab in addition to routine treatment. Within few days, there was significant symptomatic improvement. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient need no oxygen therapy. CT scans manifested that the lung lesion opacity absorbed in 19 patients (90.5%). The percentage of lymphocytes in peripheral blood, which decreased in 85.0% patients (17/20) before treatment (mean,  $15.52 \pm 8.89\%$ ), returned to normal in 52.6% patients (10/19) on the fifth day after treatment. Abnormally elevated C-reactive protein decreased significantly in 84.2% patients (16/19). No adverse reactions were seen. Nineteen patients (90.5%) were discharged on average 13.5 days after the treatment with tocilizumab and the rest were recovering well. Hence, Tocilizumab is an effective treatment in severe patients of COVID-19, which provided a new therapeutic strategy for this fatal infectious disease. Another trial is going on in the US where participants will receive two doses of Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours and will be assessed at

frequent intervals and primary observation to be made after 28 days of starting of treatment.<sup>34</sup>

#### Ecilizumab

It's a monoclonal antibody that binds complement factor C5 and blocks membrane attack complex formation. After proper vaccination of the patients, Soliris (Ecilizumab) will be given as : 900mg intravenously every 7 days for 4 weeks then 1200mg intravenously on 5th week followed by 1200mg intravenously every 14 days ongoing until at least 1 month after the patient has recovered from the virus. Once recovered symptomatically, the patient's blood will be collected for possible collection of antibody that may aid in making a vaccine against covid-19. Follow up at day 7, 14 and 28 will be done.<sup>35</sup>

#### Sequential oxygen therapy

Oxygen supplementation is must for patients as they might go into type 1 respiratory failure. A study showed that 18 of 35 deceased patient's has arterial oxygen content less than 60 mm Hg. Sequential oxygen therapy is currently under trial regarding choice of oxygen therapy based on severity of disease.<sup>36</sup>

#### Danoprevir

Danoprevir (Ganovo) is a potent HCV protease (NS3/4A) inhibitor which was approved and marketed in China since 2018 to treat chronic hepatitis C patients. Ritonavir is a CYP3A4 inhibitor to enhance plasma concentration of danoprevir while it also acts as a human immunodeficiency virus (HIV) protease inhibitor at high doses. The chymotrypsin-like protease of SARS-CoV-2 shares structural similarity with HCV and HIV proteases. The data from a small-sample clinical study showed that danoprevir boosted by ritonavir is safe and well tolerated in all patients. After 4 to 12-day treatment of danoprevir boosted by ritonavir, all eleven patients enrolled, two naive and nine experienced, were discharged from the hospital as they met all four conditions as follows: (1) normal body temperature for at least 3 days; (2) significantly improved respiratory symptoms; (3) lung imaging shows obvious absorption and recovery of acute exudative lesion; and (4) two consecutive RT-PCR negative tests of SARS-CoV-2 nucleotide acid (respiratory track sampling with interval at least one day). These findings suggest that repurposing danoprevir for COVID-19 is a promising therapeutic option.<sup>37</sup>

#### Immunoglobulins

Intravenous immunoglobulins are the safest immunomodulators available. It provides passive immunity. It has non specific antibodies. In 2003 epidemic of SARS in Singapore, immunoglobulins were used in the treatment of severely ill patients. One third of these patients developed venous thromboembolism with pulmonary embolism. These patients were also given low molecular weight heparin, but the adverse effect could not be contained. Immunoglobulin increase viscosity of blood hence lead to a hypercoagulable state.<sup>38</sup> A case series of 3 patients treated with immunoglobulin in a hospital at Wuhan, China have showed positive results. The first patient was given intravenous immunoglobulin (25gm/day) for 5 days. On sixth day his fever subsided. On seventh day his supplemental oxygen was taken off. His overall health improved. Oropharyngeal

swabs on sixth and seventh day were negative. Ninth day showed an improvement in his lymphocyte count. Similar approaches were taken for patient 2nd and 3rd who were tested negative on their nasal PCR within a few days.<sup>39</sup>

### FAVIPRAVIR

It is a RNA-dependent RNA polymerase (RdRp) inhibitor. It blocks replication of RNA virus. SARS-CoV-2 is a RNA virus. Favipiravir forms an active phosphoribosylated form which forms a substrate for RNA polymerase. In this way action of RNA polymerase is inhibited. A clinical trial taken in February at Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen on sample size of 80 patients seems to be showing positive results. It is in phase 3 showing superior results and lesser adverse effects than Lopinavir and Ritonavir.<sup>40</sup> Favipiravir comes in tablet form which has better patient compliance. At Zhongnan Hospital, Wuhan, China, a clinical trial on 120 patients was undertaken which showed experimental group (favipiravir) efficacy at 71.43% and that of control group (abidole) at 55.86%.<sup>41</sup>

### CD24Fc

A randomized controlled trial is undertaken in which two regimen, that of CD24Fc and placebo will be compared in severe Covid19 patients. Aggressive antiviral therapy, can control lung and intestinal infection. Covid19 patients show aggravated T cell lymphopenia which is worse than in HIV infection. Functional exhaustion of T cells, worse than HIV infection occurs. Multiorgan failure is explained by high levels of cytokine. Thus, a treatment with both anti-virals and non antivirals is necessary. CD24Fc is a biological immunomodulator. Its clinical trial is undertaken to check the inflammatory response in Covid-19. So, far in its study in phase 1 it successfully inhibited multiple inflammatory cytokines. In phase 2, which was tested on leukemia patients it eliminated acute graft versus host diseases. In phase 3 it has shown to decrease T-lymphocyte exhaustion and leukotriene infiltration of multiple organs. Thus CD24Fc seems to be at the forefront in non antiviral treatment for covid19.<sup>42</sup>

### Bromhexine-HCL

Bromhexine is a transmembrane protease serine inhibitor. A transmembrane protease activates Sglycoprotein of SARS-CoV and MERS-CoV which helps the virus to enter the host cell plasma membrane. It is under clinical trial. It will be used along with the standard treatment of Covid-19.<sup>43</sup> However its clinical trials in other respiratory disorders have shown only symptomatic benefit.<sup>44</sup>

### Darunavir and Cobicistat

Darunavir is HIV protease inhibitor. Cobicistat is cytochrome p450 inhibitor, hence it enhances pharmacokinetics and pharmacodynamics of darunavir. In Spain, clinical trial on this drug has been approved, their hypothesis behind this trial is that it can decrease viral load in mild to moderate cases of COVID19, making such cases less contagious.<sup>45</sup> According to Johnson and Johnson, Darunavir shows very few interactions with active site of SARS-CoV2 protease. Thus, it seems ineffective.<sup>46</sup> It is in its phase 3 clinical trial for COVID19 currently.

### Perfenidone

A clinical trial of perfenidone in treatment of patients with idiopathic pulmonary fibrosis at Japan was undertaken which showed promising results. Analyses of types of vital capacity changes, progression free survival time, and improvement in symptoms showed that pirfenidone was more effective in patients with mild-to-moderate lung function impairment (baseline %VC  $\geq$  70 and the lowest SpO<sub>2</sub> < 90). In the population of patients with mild-to-moderate disease, pirfenidone is especially effective in patients with desaturation during exercise which typically corresponds to the lowest baseline SpO<sub>2</sub> < 90.<sup>47</sup> In 2003, SARS patients with acute lung injury showed increase in interleukin-8. Despite hormonal treatment, in 2003 for SARS lung remained amidst high levels of inflammatory factors which lead to irreversible pulmonary fibrosis. Perfenidone shows positive results in terms of decreasing dose of hormonal treatment, anti inflammatory effect and decreasing pulmonary fibrosis. A randomized controlled trial is undertaken comprising of 294 severe and critically ill COVID19 patients to check the efficacy of perfenidone.<sup>48</sup> It is used in the treatment of idiopathic pulmonary fibrosis for its anti inflammatory effect mainly against IL-4 and IL-1B and antifibrotic action.<sup>49</sup>

### Amniotic Fluid

Lattice Biologics is exploring the efficacy of its amniotic fluid concentrate, AmnioBoost, in treating acute respiratory distress syndrome (ARDS) in COVID-19 patients. It reduces the production of pro-inflammatory cytokines while boosting the production of anti-inflammatory cytokines.<sup>50</sup>

### Carrimycin

Carrimycin is macrolide inhibitor with effects against some gram-positive bacteria and in vitro effects on Mycobacterium tuberculosis and already marketed for therapeutic indications including respiratory tract infections, suppurative otitis media, and acute skin and soft tissue infection. The efficacy of this drug for COVID-19 treatment is under phase 4 clinical trial, carried out by Beijing YouAn Hospital, Capital Medical University in 520 patients. In this trial, efficacy of carrimycin is compared with one of lopinavir/ritonavir tablets or Arbidol or chloroquine phosphate. The result of the study is awaited.<sup>1, 3</sup> Whereas in another study comparison is made with hydroxychloroquine.<sup>2</sup> To conclude, the efficacy of this drug is under clinical trials.<sup>51, 52, 53</sup>

Dose: 0.4 mg p.o. after meal OD 7 days for mild type, 10 days for ordinary type, and 14 days for severe and critical patients.

### FINGOLIMOD

Oral fingolimod (Gilenya™), a sphingosine 1-phosphate (S1P) receptor agonist, is the first oral agent in disease-modifying therapies (DMTs), used in treatment of multiple sclerosis in US and EU. After rapidly converting into the active moiety S-fingolimod-phosphate and binding to S1P receptors in vivo, it leads sequestration of lymphocytes in the lymph nodes and preventing their egress into the peripheral circulation. This results into decrease in infiltration of autoaggressive lymphocytes into the CNS. As a functional antagonist, by binding to S1P receptors it

downregulates S1P receptors on the lymphocyte cell surface by their internalization and degradation.<sup>54</sup> First Affiliated Hospital of Fujian Medical University carried out the study (under phase 2 trial) of efficacy of Fingolimod in the Treatment of New Coronavirus Pneumonia (COVID-19)<sup>55</sup>. In which patients were given 0.5 mg Fingolimod for 3 days and improvement is compared with baseline xray after 5 days of treatment.<sup>5</sup> However, The MS Society's medical advisors group, UK, have agreed that patients taking fingolimod have chances of having more severe viral and other infections, including COVID-19, but discontinuation can cause rebound MS disease activity, which would outweigh the risks of the virus in many cases.<sup>56</sup>

Dose: Fingolimod 0.5 mg orally once daily, for three consecutive days.

#### **TLR 2/6/9 agonist PUL-042<sup>7</sup>**

A solution consisting of a combination of two toll-like receptor (TLR) ligands: Pam2CSK4 acetate (Pam2), and oligodeoxynucleotide (ODN) M362. After inhalation of the PUL-042 solution, its components bind and activate TLRs on lung epithelial cells; induces the epithelial cells to produce peptides and reactive oxygen species (ROS) against pathogens, including bacteria, fungi and viruses present in the lungs. M362 and Pam2CSK4, through their agonist activity on TLR9 and TLR2/6 respectively, recognize pathogen and activate of innate immunity, thus prevent pulmonary infection.<sup>57</sup> The study to know the effect of PUL-042 Inhalation Solution in COVID-19 treatment, is designed to check the effect of this treatment on day 14 and day 28 after treating patients with this drug 3 times over a one week period, comparing with placebo.<sup>58</sup>

Dose: PUL-042 Inhalation Solution 20.3 µg Pam2: 29.8 µg ODN/mL (50 µg PUL-042) given by nebulization on study days 1, 3 and 6<sup>58</sup>

#### **Nitric Oxide Inhalation Therapy**

Nitric oxide (NO) is an important signaling molecule between cells and has antimicrobial activity against several bacteria, protozoa and some viruses. The up-regulation of iNOS is common during an infection, and it is known that some viruses and bacteria are either inhibited or stimulated by increased levels of NO.<sup>59</sup>

The study published in American Society for Microbiology Journals, demonstrated that *S*-nitroso-*N*-acetylpenicillamine (an organic NO donor), significantly inhibits the replication cycle of SARS CoV during the early steps of infection, via inducible nitric oxide synthase, suggesting its antiviral effect, in addition to inhibition viral protein and RNA synthesis.<sup>9</sup> In another study<sup>10</sup>, *S*-nitroso-*N*-acetylpenicillamine (SNAP) and sodium nitroprusside (SNP), were tested in a broad range of concentrations. However, no anti-SARS-CoV effect could be detected for SNP and NAP.<sup>60</sup> A clinical trial is carried out to know the efficacy of Nitric Oxide Gas Inhalation Therapy for Severe Acute Respiratory Syndrome Due to COVID-19<sup>61</sup>, designed to assess whether inhaled NO improves survival in patients affected with severe COVID-2019 and aimed to prevent progression of the disease. On the basis of data from 2004 SARS-CoV outbreak, and similarities between genomes of

SARS-CoV and COVID-19 viruses, this trial is carried out. Patients were treated with NO inhalation according prescribed dosage and outcome of treatment assessed after 14 days, comparing with controls.<sup>61</sup> Therapeutic guidelines suggest that inhaled NO may be considered in ARDS patients with severe hypoxemia; however, routine use not recommended.<sup>12</sup> Although no specific data available for treatment of COVID-19, a clinical trial assessing effect of inhaled nitric oxide for mild/moderate COVID-19 is underway (NCT04305457).<sup>62</sup>

In conclusion, although there is no confirmatory data available about effect of inhaled NO therapy in COVID-19 infection, on the basis of data available from 2003, 2004 and 2005 SARS-CoV infections, FDA approved emergency expanded access of inhaled nitric oxide delivery system to be used for the treatment of COVID-19.<sup>62</sup>

#### **Corticosteroid**

Methylprednisolone has already been used in COVID-19 patients in combination with antibiotics, oseltamivir, and oxygen therapy. There have been varying opinions on the use of corticosteroids in the treatment of COVID-19. Long et. al. in their study had found corticosteroid therapy to be beneficial in the treatment of SARS-CoV patients, and was found to significantly prolong the survival time. However, in other studies, the use of d corticosteroids in the early stages of SARS-CoV infection were described with increasing values of viral load. In contrast, studies pertaining to corticosteroid in the adjuvant therapy for MERS-CoV infection was not found to be efficacious.<sup>68</sup>

#### **Thalidomide**

Thalidomide has been proved to be safe and effective in a variety of clinical conditions including in IPF, severe H1N1 influenza lung injury and paraquat poisoning lung injury. The drug has a broad range of effects: anti-inflammatory, anti-fibrotic, anti-angiogenesis, and immune regulation. In a recent case report by Chen C. et. al., a combination of Thalidomide with low-dose glucocorticoid was used in the treatment of a case of severe COVID-19 pneumonia. They reported that this treatment reduced the pulmonary symptoms and also significantly reduced the elevated inflammatory cytokines.<sup>69, 70, 71</sup>

#### **Xiyanping**

Xiyanping in combination with conventional treatment had shown good results in the treatment of H1N1. The injection of the drug has anti-inflammatory and immune regulation effects.<sup>72</sup>

#### **Vitamin C Infusion**

Various studies have demonstrated benefits of Vitamin C in the management of sepsis and septic shock. The proposed mechanism of action of Vitamin C is its immunosuppressive effects. It acts as an anti-oxidant as well as pro-oxidant. Some studies have demonstrated association between Vitamin C deficiency with increased risk and severity of influenza infections.<sup>73</sup>

#### **Streptokinase vs Unfractionated Heparin nebulisation**

In ARDS, intra-alveolar clotting worsens hypoxemia. Heparin and Streptokinase with their anticoagulant effects



may help with the alveolar re-expansion. The effects of the drugs were compared in one study.<sup>74</sup>

### Tetrandrine

Tetrandrine is a natural compound extracted from the plant *Radix stephaniatetrandrae*. It has been used as a Traditional Chinese Medicine for a variety of conditions. It has been shown to have anti-inflammatory, immunologic and anti-allergic effects. The compound has been demonstrated to inhibit the expression of HCoV-OC43 spike and nucleocapsid protein and immunomodulation. These effects result from the non-selective calcium channel inhibition and actions on the G1 phase of the cell cycle. Additionally, it also decreases the plasma glucose concentration by increasing the uptake by the hepatocytes for glycogen synthesis. The capacity of Tetrandrine to prevent Cytokine Storm and other serious consequences comes from the recent reports of it being a possible potent inhibitor of various proinflammatory Th1, Th2 and Th17 responses in LPS-challenged mice. Thus, making Tetrandrine a potential candidate drug for the treatment of COVID-19. Prior research has supported the inhibitory effects of Tetrandrine on fibroblasts, which can be employed to prevent pulmonary fibrosis.<sup>75, 76, 77</sup>

### Safe drugs in pregnancy

Pregnant women could be more susceptible to COVID-19 infection than the general population because of immunocompromised status and physiological adaptive changes during pregnancy, but there is a few data available for assessment and management of pregnant women infected with COVID-19. In *The Lancet Infectious Diseases*, Nan Yu and colleagues reported some indications for clinical assessment and management of pregnant women with COVID-19, but how to manage pregnant women infected with COVID-19 is still unclear.<sup>63</sup> WHO guidance and some clinical evidence does not recommend the use of corticosteroids for COVID-19. Solid evidences are needed to provide basis to use drugs in pregnant women.<sup>63</sup> According to interim guidance issued by WHO and CDC on managing COVID-19, drawn on experience from previous coronavirus outbreaks<sup>64</sup>, isolation and investigation of suspected women done with admission of infected women into negative pressure isolation ward, where they should be categorized according to severity and treated accordingly. In China, patients are treated with Alpha-interferon inhalation (5 million U each time for adults, add 2 ml of sterile water for injection twice daily) after informing the risk of hindering fetal growth and development in early pregnancy. Lopinavir / ritonavir (200 mg / 50 mg, each capsule) 2 capsules each time, twice daily also given. Treatment plan also recommends the use of methylprednisolone 1~2 mg/kg/day for a short period of time (3 ~ 5 days) in specific situation; however the effects of glucocorticoids on fetuses in 2019-nCoV infected pregnant women require detailed discussion.<sup>65</sup>

American Journal of Obstetrics & Gynecology has also published general principles for management of COVID-19 during pregnancy, but all guidance need to be revised as additional data on pregnant women with COVID-19 become available.<sup>66</sup> In another article of American Journal of Obstetrics & Gynecology, has described current approach

for treatment of COVID-19 in pregnancy.<sup>67</sup> Mechanical ventilation given achieving higher maternal oxygen (target PaO<sub>2</sub> > 70 mmHg instead of 55 – 80 mmHg) and lower carbon dioxide levels (target PaCO<sub>2</sub> 28 – 32 mmHg) to maintain placental perfusion and prevent fetal hypoxemia and acidosis. It also concur with the WHO recommendation against the routine use of systemic corticosteroids, as it delays viral clearance with no survival benefit. However, in cases of expected preterm delivery, the decision for using corticosteroids for fetal maturity and to minimize per partum complications should be made by treating doctor only. Remdesivir appears to be safe in human pregnancies and phase 3 trials evaluating efficacy in COVID-19 are currently underway in the United States and China. Although chloroquine and its metabolites cross the placenta, it may be safely used in all trimesters of pregnancy without increasing risk of adverse perinatal outcomes. However, because of large volume of distribution and lower plasma drug concentrations in pregnancy, this drug needs a higher dose in COVID-19 (at least 500 mg twice daily) keeping in mind about side effects of higher doses. Although without solid basis of use in pregnant women with respiratory infections, LPV/r is known to be safe from an analysis of data of LPV/r exposure in HIV-positive pregnancies which shows no increase in the risk of fetal anomalies, preterm birth or low birth weight infants. However, ribavirin is teratogenic as it induces miscarriage, craniofacial and limb defects in the embryos of pregnant mice exposed to doses exceeding 25 mg/kg, and should be avoided, especially in early pregnancy. Similarly, baricitinib, a Janus kinase inhibitor, a potential drug for COVID-19 treatment, is contraindicated in pregnancy as animal studies have demonstrated embryo toxicity. Presently, vaccines for prevention of COVID-19 infections in pregnancy are under trials.<sup>67</sup>

## 2. Conclusion

We can not compare efficacy of one drug to another by reviewing literature as everything is under trial. In our set up we are using hydroxychloroquin, azithromycin, oseltamivir, low molecular weight heparin. Prone position is effective but didnt improve outcome in critically ill patients. ARDS protocol thought to be helpful but not improving outcome. Some believes ARDS protocol is instead damaging to such patient. Plasma therapy is currently under trial. ECMO is believed to be effective. Prognosis is very bad in patients who require Invasive or Noninvasive ventilation. As of now, any drug is not very much efficacious in such patients. In the upcoming era, vaccine might help.

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