Anti-corona Drugs: Current Scenario

In late December 2019, an outbreak of an emerging disease (coronavirus disease of 2019 [COVID-19]) due to a novel coronavirus (named SARS-CoV-2 latter) started in Wuhan, China, and rapidly spread in China and outside. The World Health Organization (WHO) declared the epidemic of COVID-19 as a pandemic on March 12, 2020. The overall case-fatality rate is about 2.3% but reaches 8.0% in patients aged 70–79 years and 14.8% in those aged >80 years.

The number of people diagnosed with COVID-19 worldwide crossed the one and half million mark on April 10, 2020; the case fatality rate across 204 countries and territories was 5.2%.[1]

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

Infected patients should receive supportive care to help alleviate symptoms. Vital organ function should be supported in severe cases. There is little empirical evidence to guide the management of COVID-19. However, with 80,000 new cases being confirmed daily and the rate still increasing, clinicians taking care of patients with COVID-19 need guidance now. The suggestions mentioned here are based on scarce direct evidence, indirect evidence, and clinical observations. The goal is to improve outcomes and facilitate research by standardizing care. The suggestions provided in this document should never be considered mandates, as no suggestion can incorporate all potential clinical circumstances. The suggestions are interim guidance and will be reevaluated as evidence accumulates.

Numerous collaborative efforts to discover and evaluate the effectiveness of antivirals (e.g., remdesivir), immunotherapies (e.g., hydroxychloroquine, sarilumab), monoclonal antibodies, and vaccines have rapidly emerged. The enthusiasm to try new therapies during outbreaks must be balanced against ethical and scientific safeguards. Although expert guidance can be sought from local or international societies, patients treated with experimental therapies should be enrolled in a clinical study when possible.

Vaccines

No vaccine is currently available for SARS-CoV-2. Avoidance is the principal method of deterrence. A phase 1 clinical trial is now planned for an experimental vaccine against SARS-CoV-2, mRNA-1273, by Moderna.

Antiviral Therapy

Lopinavir/ritonavir

The guidelines of the Chinese National Health Commission recommend aerosolized inhalation of interferon-β (IFNβ) and lopinavir/ritonavir.[2]

The specific therapeutic value and safety of lopinavir/ritonavir in patients with COVID-19 are under investigation.

In a randomized, controlled, open-label trial of hospitalized adults (n = 199) with confirmed SARS-CoV-2 infection, recruited patients had an oxygen saturation of 94% or less on ambient air or PaO2 of less than 300 mm Hg and were receiving a range of ventilatory support modes (e.g., no support, mechanical ventilation, extracorporeal membrane oxygenation [ECMO]). These patients were randomized to receive ritonavir/lopinavir 400 mg/100 mg PO BID for 14 days added to standard care (n = 99) or standard care alone (n = 100). Results showed that time to clinical improvement did not differ between the two groups (median, 16 days). The mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs. 25%) but did not reach statistical significance. In hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care. Future trials in patients with severe illness may help to confirm or exclude the possibility of a treatment benefit.[3]

An editorial accompanies this study that is informative in regard to the extraordinary circumstances of conducting such a study in the midst of the outbreak.[4]

The WHO has not taken a position on the use of lopnavir-ritonavir in COVID-19 but its SOLIDARITY trial includes a lopinavir ritonavir arm. The CDC states that "lopinavir-ritonavir did not show promise for the treatment of hospitalized COVID-19 patients with pneumonia in a recent clinical trial in China. This trial was underpowered…" The FDA has not taken a position on the use of lopinavir-ritonavir in COVID-19. The Surviving Sepsis Campaign made a weak recommendation against the routine use of lopinavir-ritonavir.[5]

Remdesivir

The broad-spectrum antiviral agent remdesivir (GS-5734; Gilead Sciences) is a nucleotide analog prodrug. Several phases 3 clinical trials are underway for testing remdesivir for use in COVID-19 in the United States, South Korea, and China. They were deemed to be the most promising candidate drug by experts.

An *in vitro* study showed that the antiviral activity of remdesivir plus IFNβ was superior to that of lopinavir/ritonavir (LPV/RTV; Kaletra, Aluvia; AbbVie Corporation). Prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology in mice, whereas LPV/RTV-IFNb slightly reduced viral loads without affecting other disease parameters. Therapeutic LPV/RTV-IFNb improved

pulmonary function but did not reduce virus replication or severe lung pathology.[6]

Successful treatment with remdesivir has been reported in a patient with COVID-19; a clinical trial on the efficacy of remdesivir in patients with COVID-19 is currently underway in China (NCT0425266; NCT04257656) and is expected to be completed in April 2020. No peer-reviewed, published safety data are available for SARS-CoV-2. The WHO has not taken a position on the use of remdesivir in COVID-19 but its SOLIDARITY trial includes a remdesivir arm. The CDC has not taken a position on remdesivir but describes options for obtaining it for hospitalized patients with COVID-19 and pneumonia. The FDA reports that it has been working with the maker of remdesivir to find multiple pathways to study the drug under the FDA's investigational new drug requirements and to provide the drug to patients under emergency use. The Surviving Sepsis Campaign made no recommendation for or against remdesivir due to insufficient evidence.[5]

Chloroquine and hydroxychloroquine

Chloroquine phosphate has been shown to have some efficacy against COVID-19-associated pneumonia in multicenter clinical trials conducted in China.[7]

According to a consensus statement from a multicenter collaboration group in China, chloroquine phosphate 500-mg twice daily in tablet form for 10 days may be considered in patients with COVID-19 pneumonia[8]

Wang *et al*.[9] reported that chloroquine effectively inhibits SARS-CoV-2 *in vitro*.

Hydroxychloroquine and chloroquine have been shown to have *in vitro* activity against SARS-CoV-2, with hydroxychloroquine being more potent.[9,10] Clinical trials, however, provide an inconsistent message. Small controlled clinical trials from more than 10 hospitals in China reportedly indicate that chloroquine is superior to controls in preventing pneumonia, improving lung imaging findings, hastening conversion to a virus-negative state, and shortening the duration of disease.[11] However, two of the trials are now publicly available, and they have important limitations: in a negative trial, both arms included patients who had undergone treatment with anti-viral drugs[12] and, in a positive trial, the arms of the trial had important baseline differences.[13] A small controlled trial from France reported that hydroxychloroquine hastens conversion to a virus-negative state, but important limitations included a lack of patients with severe illness, lack of blinding, no randomization, and loss to follow-up.[14] The results are notable for a shift toward treatment with hydroxychloroquine or chloroquine as the severity of COVID-19 increased, indicating that the perceived balance of potential benefits to harms changed as the severity of illness increased.

The WHO has warned against the use of medications that have not been proven in an RCT; its SOLIDARITY trial includes a chloroquine arm. The CDC says, "There are no currently available data from RCTs to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection." The US FDA stated that there is insufficient evidence to support treatment of COVID-19 with hydroxychloroquine or chloroquine, but issued an emergency-use authorization to allow both donated drugs "to be distributed and prescribed by doctors to patients with COVID-19, as appropriate, when a clinical trial is not available or feasible." The Surviving Sepsis Campaign made no recommendation for or against hydroxychloroquine or chloroquine due to insufficient evidence.[5]

The National Taskforce for COVID-19 from India recommended the use of hydroxychloroquine for prophylaxis of SARS-CoV-2 infection for:
1. Asymptomatic healthcare workers having direct contact with suspected or confirmed cases of COVID-19
2. Asymptomatic family contacts of confirmed cases.

This recommendation is subject to the following conditions:
1. Hydroxychloroquine is found to be effective against coronavirus in laboratory studies and in-vivo studies. Currently, there is no direct evidence about its role in prophylaxis. The recommendation for the use of hydroxychloroquine as a prophylactic agent against SARS-CoV-2 infection is based on empirical evidence, as well as risk-benefit consideration, and its safety profile
2. Dose:
   a. Asymptomatic healthcare workers: 400 mg per week for 8 weeks
   b. Asymptomatic family contacts of confirmed cases: 400 mg per week for 4 weeks.
4. The drug is not recommended for children under 15 years of age
5. The drug is contraindicated in persons with significant hepatic or renal dysfunction and those with known hypersensitivity to the 4-aminoquinoline compound.

Glucocorticoids

Patients with COVID-19 have elevated levels of pro-inflammatory cytokines and other inflammatory biomarkers, leading some clinicians to postulate that systemic corticosteroid therapy may be beneficial. In a retrospective study of patients with SARS-CoV and sepsis, steroids, at a mean daily dose of 105.3 _ 86.1 mg in 147 of 249 noncritical patients (59.0%), reduced mortality rate and shortened duration of hospitalization, whereas 121 of 152 critical patients (79.6%) received corticosteroids at a mean daily dose of 133.5 _ 102.3 mg, and 25 died.[15]

A subsequent retrospective, observational study of 309 patients with MERS showed that those who received

high-dose steroids were more likely to require mechanical ventilation, vasopressors, and RRT.[13]

A retrospective study of 84 patients with ARDS associated with COVID-19 found lower mortality in those treated with methylprednisolone, but the findings are limited by the observational design of the study, small sample size, and possible confounders.[16]

In a meta-analysis of corticosteroid use in patients with SARS, four studies provided conclusive evidence of harm (psychosis, diabetes, avascular necrosis, and delayed viral clearance).[17]

Therefore, the use of steroids is controversial and not recommended by the World Health Organization because of potential inhibition of viral clearance and prolongation of the duration of viremia.[18]

The WHO says that clinicians should "not routinely give systemic corticosteroids for the treatment of viral pneumonia outside clinical trials." The CDC says "corticosteroids should be avoided unless indicated for other reasons, such as management of chronic obstructive pulmonary disease exacerbation or septic shock." The FDA has not taken a position on the use of systemic corticosteroids in COVID-19. The Surviving Sepsis Campaign made a weak recommendation against systemic corticosteroids in mechanically ventilated COVID-19 patients without ARDS, but a weak recommendation for systemic corticosteroids in mechanically ventilated COVID-19 patients with ARDS.[5]

Convalescent plasma

Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. This has been noted in Ebola and Middle East respiratory syndrome viral infections.[19,20]

One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viremia.

Preliminary clinical studies in China have shown that early application of convalescent plasma in patients with COVID-19 could accelerate clinical recovery.[21]

Findings from a preliminary study of five severely ill patients with COVID-19 who were treated in the Shenzhen Third People's Hospital, China, using plasma from recovered individuals.[22] All patients had severe respiratory failure and were receiving mechanical ventilation; one needed ECMO and two had bacterial and/or fungal pneumonia. Four patients without coexisting diseases received convalescent plasma around hospital day 20, and a patient with hypertension and mitral valve insufficiency received the plasma transfusion on day 10. The donor plasma had demonstrable IgG and IgM anti-SARS-CoV-19 antibodies and neutralized the virus *in vitro* cultures.

Although these patients continued to receive antiviral treatment primarily with lopinavir/ritonavir and IFN, the use of convalescent plasma may have contributed to their recovery because the clinical status of all patients had improvement approximately 1 week after transfusion, as evidenced by normalization of body temperature as well as improvements in SOFA scores and PAO2/FIO2 ratio. In addition, the patients' neutralizing antibody titers increased, and respiratory samples tested negative for SARS-CoV-2 between 1 and 12 days after transfusion. Even though the cases in this report by Shen *et al.* are compelling and well-studied, this investigation has important limitations that are characteristic of other "anecdotal" case series. The intervention, administration of convalescent plasma, was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with outcomes in a control group of patients who did not receive the intervention. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without this therapy. In addition, patients received numerous other therapies (including antiviral agents and steroids), making it impossible to disentangle the specific contribution of convalescent plasma to the clinical course or outcomes. Moreover, convalescent plasma was administered up to 3 weeks after hospital admission, and it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes. Despite these limitations, the study does provide some evidence to support the possibility of evaluating this well-known therapy in more rigorous investigations involving patients with COVID-19 and severe illness. No adverse events were reported among patients receiving convalescent plasma.

Despite the potential utility of passive antibody treatments, there have been few concerted efforts to use them as initial therapies against emerging and pandemic infectious threats. The absence of large trials certainly contributes to the hesitancy to employ this treatment Both academic,[23] and industry groups are beginning to investigate the efficacy of passive antibody therapies for COVID-19 infection.

Currently two trials, an open-label, nonrandomized clinical trial NCT04264858) and a multicenter, randomized, and parallel controlled trial (ChiCTR2000029757) on the efficacy of convalescent plasma in patients with COVID-19, is underway in China.

The US FDA has approved the use of plasma from recovered patients to treat people who are critically ill with COVID-19, provided that doctors get approval over the telephone.[24] FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. The guidance also provides recommendations

to blood establishments on the collection of COVID-19 convalescent plasma.[25]

Monoclonal antibody

A monoclonal antibody against COVID-19 has not yet been developed. Monoclonal antibody directed against the RBD domain of the S Q7 protein of MERS-CoV has been found to have neutralizing activities in plaque assays *in vitro*.[26]

Tocilizumab

Tocilizumab, a monoclonal antibody against the IL-6 receptor, has achieved encouraging preliminary clinical results. Patients with COVID-19 have elevated levels of the pro-inflammatory cytokine, IL-6, with the most severely ill patients showing the highest levels. Tocilizumab antibody that has proven effective in other IL-6 mediated diseases. It is recommended by China's National Health Commission for use in COVID-19 patients with elevated IL-6 levels. The WHO, CDC, and FDA have not taken a position on the use of tocilizumab in COVID-19, although the FDA approved an RCT comparing tocilizumab to standard care. The Surviving Sepsis Campaign made no recommendation for or against tocilizumab due to insufficient evidence.[5] The safety and efficacy of tocilizumab in COVID-19 infection are undergoing evaluation by a multicenter randomized controlled trial (ChiCTR2000029765).

Hydroxychloroquine and azithromycin

In an open-label non-randomized French clinical trial confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600 mg 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. Untreated patients from another center and cases refusing the protocol were included as negative controls. The presence and absence of a virus at Day6-post inclusion was considered the end point. 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. Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.[14]

Favipiravir

It is a RNA-dependent RNA polymerase inhibitor. It is the Japanese flu drug**.** Hypothesized to have an antiviral action on SARS-CoV-2 (RNA virus); multiple clinical studies are underway for SARS-CoV-2.

A Chinese trail used Favipravir on 340 patients and showed viral disappearance in 4 days compared to the ones who did not get the drug. However, this trial has been taken off the internet for reasons not specified. No peer-reviewed published efficacy data available for SARS-CoV-2.Preliminary, unpublished trial data suggest a more potent antiviral action with favipiravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results No peer-reviewed, published safety data available for SARS-CoV-2; preliminary, unpublished trial data suggest fewer adverse events with Favipravir compared with lopinavir–ritonavir, but caution is advised in interpreting these results.[27]

Secondary hemophagocytic lymphohistiocytosis (sHLH) may be responsible for some of the deaths in adult patients with severe COVID19. Experience of lowvolume plasma exchange (PLEX) with lowdose steroid in the treatment of adult patients with sHLH and acute liver failure caused by dengue virus and other nonviral triggers and how this may be effective in the management of severe COVID19 is dealt in this study from CMC, Vellore. sHLH is poorly understood and without effective treatment. Endothelium of the capillaries of the lungs and kidneys and of liver sinusoids does not express von Willebrand factor (VWF) in health and is where most macrophages are located. Plasma VWF levels are high in sHLH and require clearance by macrophages, which when activated enlarge and likely block the lumen. Current histology studies neither appreciate microcirculatory sludge nor display endothelial–macrophage interactions. The authors hypothesize that lowvolume PLEX and lowdose steroid may reverse sHLH and improve survival in severe COVID19 patients with acute lung injury.[28]

The COVID-19 outbreak is a stark reminder of the ongoing challenge of emerging and reemerging infectious pathogens and the need for constant surveillance, prompt diagnosis, and robust research to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures.

No drugs or biologics have been proven to be effective for the prevention or treatment of COVID-19. Numerous antiviral agents, immunotherapies, and vaccines are being investigated and developed as potential therapies.

Most patients with COVID-19 in China were given empirical broad-spectrum antibiotics and many, oseltamivir, because laboratory diagnosis of COVID-19 takes time, and distinguishing the disease from other bacterial and viral pneumonias is often difficult. Any empirical antibiotic and anti-influenza therapy should be rapidly de-escalated based on microbiology test results and clinical response.

The trade-off between waiting for evidence before deciding whether to administer a therapy and using a therapy while awaiting evidence isn't unique; however, it is magnified by the urgency of a pandemic.[29] The tension is probably best

solved by creating evidence during routine patient care, while awaiting clinical trial results.

In conclusion, empirical evidence, particularly randomized trials, are desperately needed to guide therapy. Supportive care remains the mainstay of treatment and social distancing remains an important part of prevention. The suggestions provided in this document will be periodically reevaluated as new evidence emerges and modified accordingly.

When it comes to findings, the COVID-19 train is an express, whereas the rigorous science coach is a local. Until that local arrives at its final destination, it may be wise to label all this research—preprints, peer-reviewed papers— with a black-box warning: "There is some evidence for this now. It will likely turn out to be at least partially wrong."

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Conflicts of interest

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