



## Medical management of COVID-19 clinic

Neha Mehta, Renli Qiao<sup>✉</sup>

*Division of Pulmonary, Critical Care and Sleep Medicine, Department of Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA 90033, USA.*

### Abstract

The start of the global pandemic secondary to the novel SARS-CoV-2 virus was a time of uncertainty and fear as it claimed the lives of many across the world. Since then, there has been a plethora of research designs and trials in order to understand what we can do to stop the spread of the disease. Scientists and health care providers have utilized old medications and revamped them for current use such as convalescent plasma and steroids, as well as creating novel therapeutics, some with promising results. In this article, we review the major therapeutic options currently available and look into what the future still holds in order to further our understanding of this mysterious disease.

**Keywords:** COVID-19, treatment, steroids, remdesivir, vaccine

### Introduction

In its beginning, the COVID-19 global pandemic was a time of grave uncertainty, fear and hopelessness. We have not felt such vulnerability and mass loss of human life since the 1918 H1N1 influenza A pandemic. As the healthcare system has been overwhelmed with cases, our collective knowledge increases daily and new light is shed on therapeutic options for these patients. Sadly, treatments that held initial promise have proved to be useless or even harmful rather than beneficial<sup>[1]</sup>. The search, however, continues and an awe-inspiring breadth of literature is available in an unprecedented speed and volume. There are currently more than 2500 clinical trials registered on the topic of COVID-19<sup>[2]</sup>. As of now, there are no medications approved for use to prevent or cure COVID-19, but

what is available is focused on supportive care and improvement in secondary outcomes. Although we still have much to learn, this review article will summarize what we know so far and what is yet to come.

COVID-19 leads to severe disease requiring oxygen support in approximately 15% of patients, while 5% go on to develop critical disease. In critical disease, patients are at risk of developing many complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and multi-organ failure<sup>[3]</sup>. Understanding the mechanism of COVID-19 disease allows us to focus on more targeted treatments with the goal of improving patient outcomes.

It is postulated that there are three distinct phases of the disease: a viral response phase, pulmonary phase, and host immune response phase<sup>[4]</sup>. In the early stages,

<sup>✉</sup>Corresponding author: Renli Qiao, Division of Pulmonary, Critical Care and Sleep Medicine, University of Southern California, 2020 Zonal Avenue, IRD 700, Los Angeles, CA 90033, USA. Tel/Fax: +1-323-409-7184/+1-323-226-2738, E-mail: [rqiao@med.usc.edu](mailto:rqiao@med.usc.edu).

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rapid viral replication occurs with a high viral load; the body responds to this with the innate immune system. At this point in the disease, there is theoretical benefit for antivirals. During the later phases, the adaptive immune response is initiated which decreases viral titers but has a potential to induce tissue damage by a dysregulated immune system. In some patients this has a propensity to devolve into a cytokine release syndrome<sup>[5]</sup>.

Roncati *et al* propose a type 3 hyperimmune response as the underlying pathophysiology of this syndrome<sup>[6]</sup>. In brief, they have noted a preferential Th2 response with minimal Th1, Tc response in intensive care unit patients with COVID-19. This finding suggests an unchecked production of antigen-antibody complexes which cannot be cleared effectively by the innate system. The immune complexes subsequently deposit and wreak havoc throughout the body, leading to hypothesis that interrupting the inflammatory cascade would modify the course of the disease.

Given there is no cure yet, additional supportive therapies that target secondary effects as a result of COVID-19 include anticoagulation in the appropriate setting, prone positioning, and vaccine development.

### Hydroxychloroquine/chloroquine

At the start of the pandemic, we saw promise in hydroxychloroquine and chloroquine, so much that it led the FDA to emergently approve these drugs for SARS-CoV-2 patients and led to supply shortages. These are antimalarial drugs that have long been commonly used in rheumatologic conditions. They have both been reported to inhibit SARS-CoV-2 *in vitro*<sup>[7]</sup> but whether it might work as an antiviral by inhibiting cell entry or an immunomodulator is unclear. The initial data regarding the use of hydroxychloroquine with or without azithromycin came from low powered observational studies that offered initial promise of benefit<sup>[8]</sup>. However, larger conducted studies, both randomized and observational, showed that not only there is no benefit in hospitalized patients, but there is a potential for actual harm due to ventricular arrhythmias<sup>[9]</sup>. The World Health Organization (WHO) is conducting a large SOLIDARITY trial evaluating various treatments for COVID-19 and has recently terminated the hydroxychloroquine arm due to lack of benefit in preliminary data. Currently, the FDA has revoked emergency approval for hydroxychloroquine and chloroquine for COVID-19. Yet, in a more recent retrospective analysis, the Henry Ford Task Forces

reported that use of hydroxychloroquine alone and in combination with azithromycin was associated with a significant reduction in COVID-19 associated mortality, but as the authors cautioned, prospective trials are needed to examine this impact<sup>[10]</sup>.

### Lopinavir/ritonavir

Another proposed option was use of combination of protease inhibitors, lopinavir and ritonavir, that have been used primarily in HIV infection. Some animal studies suggested that this combination may have had activity against MERS-CoV<sup>[11]</sup>. However, human trials failed to show benefit. In a randomized trial of 199 patients with severe disease, the use of the medications given twice a day for 14 days as compared to standard of care, did not decrease the time to clinical improvement<sup>[12]</sup>. Therefore, this option is no longer considered as a therapeutic agent in the treatment of COVID-19.

### Antiviral agents

In early report of a single case, dramatic improvement in severe COVID-19 disease was attributed (probably inaccurately) to the use of remdesivir and was published in leading medical journal<sup>[13]</sup>. Development of remdesivir as an antiviral agent was based on intriguing pharmacology and virology<sup>[14]</sup>. However, remdesivir has failed previously in clinical trials for the treatment of EBOLA and again for MERS. The clinical trial for COVID-19 was started very early when the COVID-19 spread was almost limited to Wuhan, China<sup>[15]</sup>. Seemingly impossibly coincident, the negative result of the first trial<sup>[15]</sup> was not published until the same day when positive effect was announced from another trial. The positive effect was based on secondary parameter in that the length of hospital stay in COVID-19 patients was shortened from 15 to 11 days<sup>[16]</sup>.

Favipiravir, a viral RNA polymerase inhibitor, was also shown to be a potential anti-viral agent for SARS-CoV-2<sup>[17]</sup>.

### Convalescent plasma and monoclonal antibodies

An alternative but not novel concept is the use of convalescent plasma for targeting viremia. Its concept of artificial acquired passive immunity dates back to the 1880s where collecting plasma from patients who recovered from an infection, such as diphtheria, and thereafter developed humoral immunity with pathogen

specific antibodies<sup>[18]</sup>. Administering the plasma of these patients into the affected host allows for neutralization of the infection and eventual eradication from the blood circulation. This therapy is no longer used for bacterial infections since the advent of antibiotics, but its role in viral infections remains ongoing. The evidence supporting its use is limited and subject to many design biases, but a meta-analysis of 32 studies looking at its role with SARS-CoV-2 and influenza showed evidence for reduced mortality when given early in the disease course<sup>[19]</sup>. Data supporting convalescent plasma use in COVID-19 is also currently limited, but many trials are undergoing active enrollment. In one study examining 5000 patients with severe COVID-19 disease who received one dose of plasma, it showed that therapy had a good safety profile and that there were only 36 out of 5000 serious adverse events and that only 2 were definitely related to the transfusion<sup>[20]</sup>. Additional trials show evidence of improvement in chest imaging and inflammatory markers (*i.e.* lymphocyte count, viral load, and CRP) within 7 weeks after symptom onset and no difference in those who received it after 7 weeks<sup>[21]</sup>.

Similarly, several monoclonal antibodies are being investigated for prevention and treatment of COVID-19<sup>[22]</sup>. The main target of the neutralizing antibodies is the surface spike (S) glycoprotein that mediates viral entry into host cells<sup>[22]</sup>. Many studies have reported the structure and function of neutralizing antibodies that target the receptor-binding domain (RBD) and inhibit the association the S protein and ACE2<sup>[23]</sup>. However, there is concern that this may induce resistance mutations so Chi *et al* evaluated antibodies that target non-RBD epitopes to regions of the S protein of SARS-CoV-2 from ten convalescent COVID-19 patients<sup>[23]</sup>. They unexpectedly found that there may be other important mechanisms for SARS-CoV-2 neutralization in addition to suppressing the viral interaction with the receptor which ultimately may offer more therapeutic options. Perhaps, the most intriguing implication of this line of research is that enhancement of host acquired immunity deserves attention, as development of antiviral agent has traditionally been challenging.

### **Tocilizumab**

Elevated inflammatory markers and pro-inflammatory cytokines are associated with severe COVID-19 and blocking these pathways has been proposed to prevent disease progression. One such therapy is use of interleukin-6-antagonists, of which

Tocilizumab, typically used for rheumatic diseases and cytokine release syndrome, is most studied for use in COVID-19 associated cytokine release phenomenon. Early results from the CORIMUNO-TOCI open label randomized trial from France showed that in those who received tocilizumab, the need for invasive mechanical ventilation was lower than those who did not receive the medication<sup>[24]</sup>. Dosing strategy is somewhat variable but generally includes an initial dose of IV infusion of 8 mg/kg on day 1 followed by a second infusion on day 3 if no response to initial infusion (*i.e.* no decrease in oxygen requirement). Other studies have shown that although there may be some benefit, this is coupled with increased risk for secondary infection<sup>[25]</sup>. Weighing this risk is an important consideration in choosing the appropriateness of use of this class of medications for COVID-19.

### **Glucocorticoids**

Steroids have long been studied and used in patients with critical illness and there has been much interest in their application with those with severe disease secondary to COVID-19. Initial studies suggested conflicting effects of steroids, some showing increased mortality if used too early in the disease course<sup>[26]</sup>, whereas others supported use of them in severe illness. The largest trial to date is the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial from the United Kingdom which was a randomized open label trial that demonstrated a mortality benefit using dexamethasone 6mg daily for up to 10 days in hospitalized patients with acute hypoxemic respiratory failure<sup>[27]</sup>. Investigators found death rates of 41% in ventilated patients and 20% in non-ventilated patients but requiring oxygen. In those that received dexamethasone, the death rate was reduced by one third in ventilated patients and one fifth in non-ventilated patients still requiring oxygen. No benefit was found in patients who did not require oxygen and so therefore use of steroids is not recommended for prevention or treatment of mild to moderate COVID-19.

In our own experience, methylprednisolone at 1 mg/kg in divided doses for 3 to 6 days until significant reduction in levels of inflammatory markers was seen achieved an even lower mortality in patients requiring mechanical ventilation in comparison to the mortality reported in RECOVERY trial in similar patients (Qiao *et al*, manuscript in preparation).

Additional trials are needed to help support these

findings and careful consideration needed to be given weighing the risks and benefits of use of steroids in this patient population. Based on the previous experiences from SARS-COV, the adverse effects of steroids are not benign, which may include hyperglycemia, hypertension, superinfection, and avascular necrosis<sup>[28]</sup>. These effects, however, depend on other factors including comorbidities, age, severity, dose, and duration of steroids.

### Anticoagulation

An important consideration to factor in is the predisposition to a coagulopathy in those affected with COVID-19. Multiple reports have shown increase in activation of the coagulation cascade, fibrin, fibrin degradation products leading to increased thrombosis, suggesting rates anywhere from 7% to 30%<sup>[29]</sup>. Management of the hypercoagulable state creates unique challenges in the setting of a paucity of randomized controlled trials looking at specific anticoagulation strategies that go beyond the standard indications<sup>[30]</sup>. Tremblay *et al* reported in their cohort study no statistically significant mortality benefit for patients on systemic anticoagulation for standard indications<sup>[31]</sup>. Various large societies including the CDC and the International Society on Thrombosis and Hemostasis (ISTH) have created recommendations for approaching unique situations encountered in prevention and treatment of thrombotic disease in COVID-19, weighing risks and benefits of each situation<sup>[32]</sup>. Clinicians should refer to these as well as institution specific guidelines at this time for guided decision making. Continued enrollment in clinical trials is important to help understand the best approach for these patients going forward.

### Ventilator support

As the COVID-19 is primarily a respiratory illness, this ultimately leads to a spectrum of severity of respiratory sequela from patients requiring no oxygenation, to non-invasive ventilation, to mechanical ventilation with severe ARDS. What precludes patients to these categories remains one of the greatest mysteries to date. How to support these patients through their illness from a ventilation and oxygenation standpoint is better understood but remains complex and too detailed to cover succinctly here<sup>[33]</sup>. However, one of the most common supportive treatments that has been implemented in all stages of respiratory illness has been the use of prone positioning. The use of prolonged prone positioning is

extrapolated from mechanically ventilated patients with ARDS in which prone ventilation has been shown to have mortality benefit<sup>[34]</sup>. Several mechanisms have been proposed to account for the effect of increased oxygenation which include increase in end expiratory lung volume, improved ventilation-perfusion matching, and regional changes in ventilation associated with alterations in chest wall mechanics<sup>[35]</sup>. These principles have been applied to non-ventilated patients and the use of awake prone position in small studies has been proven to increase oxygenation and has been widely adopted at many institutions across the globe due to low risk of harm<sup>[36]</sup>. How this contributes to long term outcomes as well as its role in delaying intubation remains to be seen.

### Blood purification technologies

As previously mentioned, severe COVID-19 in later stages has a propensity to devolve into a cytokine release syndrome in which uncontrolled inflammation can lead to severe multiorgan failure and even death<sup>[5]</sup>. Technologies that filter the blood to reduce levels of cytokines may help control the inflammatory response and its secondary effects. There are various types of extracorporeal blood purification systems available (*i.e.* hemoperfusion, hemofiltration, plasmapheresis) that use adsorption devices that non selectively capture molecules, such as cytokines, and filter it from the blood<sup>[37]</sup>. One such device that has received FDA Emergency Use Authorization (EUA) is CytoSorb which has been used internationally in case reports and observational trials and is currently undergoing many clinical trials to determine its true effect<sup>[38]</sup>. While there is limited evidence available currently, there is hope that this therapy may be used in addition to previously mentioned therapeutic options.

### Vaccine

Vaccine development for COVID-19 is rapidly underway and significant resource utilization is being funneled to this effort as it may be the only chance of controlling this pandemic. The impressive nature of this can be understood whereby normal vaccine development can take upwards of 5 years, whereas vaccine trials for COVID-19 are already in phase 2 and 3 with goal availability within the next year<sup>[39]</sup>. Antiviral vaccines are either gene based or protein based in which the mechanisms of these effect a variety of features including safety, immunogenicity, speed, and cost of manufacturing<sup>[40]</sup>. At the time of

writing of this article, there are currently 31 candidate vaccines in clinical evaluation and 142 candidate vaccines in preclinical evaluation<sup>[39]</sup>. The world anxiously awaits the results of these studies.

Unfortunately, in latest guidelines by both the WHO and National Institutes of Health (NIH), the above discussed agents are all recommended not to be administered outside of the context of clinical trials<sup>[41–42]</sup>. Other agents targeting angiotensin-converting enzyme 2 (ACE2) receptor system<sup>[43]</sup> or lipid metabolism<sup>[44]</sup> are in even more preliminary exploration stage. We are likely still only in the beginning of our battle with SARS-CoV-2. As cases in the USA increase, some experts argue that we are early in the first wave of the disease and cannot yet make out the haze of the shore. Others argue about the number of waves we await or a seasonal disease, accompanying influenza, bringing trouble cyclically.

We eagerly await a vaccine that would terminate the spread of this disease, but optimistic estimates note that to be more than a year away. In the meantime, we must do with what we have and currently remdesivir along with dexamethasone seem to be our most promising tools. Ultimately before a vaccine rescues us, we must rely on human behavior to be our savior mitigating exposure and infection. Truly, our most important weapons against COVID-19 are also the simplest: wearing mask and hand-washing.

## Conclusions

It has been just under a year since the start of the global pandemic. Although the virus claimed many lives at its onset, the human race has come together to understand how the virus works in order to enlist specific therapeutic targets and even a vaccine against this virus. We still have much more work to do, but as we learn more and research expands, we continue to change the reputation of SARS-CoV-2 from a deadly virus into just another virus.

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