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Editorial

# COVID-19: The Uninvited Guest in the Intensive Care Unit (ICU)

## Implications for Pharmacotherapy

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As the number of cases of COVID-19 (SARS-CoV-2) rise in the United States (US), the number of severe cases (those requiring ICU admission) rise with it. Initially, the estimate for severe cases was approximated at 5% based on experience from China.[1, 2] However, the World Health Organization's (WHO) estimate from China for severe and critical cases is near 20% (Table).[3] The primary clinical feature of COVID-19 is pneumonia, the severity of which directs the clinical course; it has been estimated that, of patients admitted to the ICU, up to half may require either invasive or non-invasive ventilatory support.[4] This has created an unprecedented situation for emergency and critical care medicine.

*Clinical manifestations*

Fever, cough and dyspnea are the most common signs of COVID-19[5]; it is a respiratory tract infection with pneumonia being the hallmark of more severe illness and the acute respiratory distress syndrome (ARDS), a serious complication and manifestation of its most critical form (Table).[5] While there are no symptoms that distinguish COVID-19 from other causes of acute hypoxemic respiratory failure,[6, 7] there appear to be distinct features (e.g., anosmia) and/or findings on chest computed tomography (e.g., patchy ground glass opacities in the lung periphery)[8] that could provide important clues, particularly if the result of a diagnostic test is unavailable. Critical illness often includes multi-organ dysfunction or failure and severe COVID-19 appears to be no different. Early reports from China cite an incidence of acute kidney injury in ~30% of patients, cardiac complications in ~23% and liver dysfunction in ~29%.[5] In addition, nausea and/or vomiting has been reported in 5% of cases and in some instances may be intractable. Complications such as cardiac arrhythmias, myocardial ischemia (with elevations in troponin) and cardiac arrest, have also been reported.[9] Patients with underlying cardiovascular disease (CVD) may be at increased risk of these complications. Patients who require mechanical ventilation represent the most critically ill and mortality has been reported as high as 62%.[5] A cytokine storm syndrome resembling a secondary hemophagocytic lymphohistiocytosis-like presentation has been identified in up to 50% of patients and may predict worsened outcomes.[10] Healthcare utilization is a major concern, as these patients often require prolonged mechanical ventilation prior to either recovery or death, leading to equipment and potential medication shortages during times of surge.

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*Respiratory and Cardiovascular Complications*

One of the most serious complications of COVID-19 is ARDS, representing a major risk factor for death.[5] The management of these patients should follow evidence-based treatment guidelines.[11, 12] This includes the use of lung-protective ventilation, conservative fluid strategies, neuromuscular blocking agents to facilitate ventilator synchrony, prone positioning as appropriate, and empirical antibiotics for suspected bacterial co-infection with aggressive de-escalation. In the setting of refractory hypoxemia, extracorporeal membrane oxygenation should be considered.

Serious cardiovascular complications can also occur and patients with underlying CVD may be at greatest risk. This may be related to the fact that COVID-19 enters cells via the angiotensin converting enzyme (ACE) 2 receptor. The concern is that in experimental studies, administration of either ACE inhibitors or angiotensin receptor blockers (ARBS) resulted in the upregulation of ACE2 expression in the heart.[13] Although these findings have not been replicated in human studies, or in the setting of COVID-19, such potential upregulation of ACE2 by ACE inhibitors or ARBs has resulted in speculation that these medications might worsen infection or predispose patients to myocardial injury. There are also preclinical data that show that ARB-induced upregulation of the ACE2 receptor lessens ARDS severity. In a preclinical model of severe acute respiratory syndrome (SARS Co-V), treatment with losartan improved angiotensin signaling, ARDS, and survival[14] and severe COVID infections are associated with low (not high) expression of ACE2.[15] In aggregate, the pre-clinical data are conflicting but it may be that a dysregulated angiotensin system, rather than a specific medication, may drive differences in outcomes. In the absence of definitive evidence, concern about the use of ACE inhibitors and ARBs was recently addressed by a joint statement from Heart Failure Society of America, the American College of Cardiology and the American Heart Association.[16] They collectively recommend that these therapies neither be withheld nor added in COVID-19 patients based on lack of human data and preclinical data suggesting benefit from their use. In the emergency department and ICU, treatment of CV complications should be managed by established therapies and when applicable, advanced cardiac life support protocols (https://www.acls.net/aclsalg.htm) should be employed. However, it may be prudent to avoid

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the use of angiotensin II for treatment of refractory shock until more information regarding the interaction between COVID-19 and the renin-angiotensin-aldosterone system is available.

*Mitigation and Treatment*

Personal protective equipment (PPE) is forefront in mitigating nosocomial infection and protecting healthcare workers. Larger hospitals are also establishing dedicated respiratory infectious containment units specifically for the treatment of COVID-19 patients whether they require mechanical ventilation or not. Staffing models for these units may preferentially include providers already recovered from the virus as the pandemic evolves, given a theoretical potential for relative immunity, though this does not mitigate the recommendations for stringent PPE practices. Pharmacists can play an important role in improving the safety of fellow healthcare practitioners entering and exiting rooms of those with COVID-19 and reduce PPE use through medication regimen optimization. As appropriate, medication administration times can be standardized to limit the number of different medication administrations throughout the day (i.e., retiming medications from 0600, 0700, and 0800 to all be administered at 0700). The use of long-acting medication formulations, when available, may also limit the number of daily required medication administrations. Additionally, subcutaneous insulin may be preferred to intravenous insulin infusions as a way to reduce frequent entry into patient rooms. Creative efforts to further reduce exposure and the need for multiple PPEs should be explored and may include positioning equipment outside of the patient room (e.g., intravenous medication infusion pumps).

Pharmacotherapy for COVID-19 is limited and treatment remains primarily supportive. At the time of the writing of this paper, no COVID-19 specific pharmacotherapies were approved by the FDA (on March 29th, the FDA authorized emergency use of chloroquine and hydroxychloroquine). Nevertheless, the gravity of the situation has led to a flurry of anecdotal pharmacotherapy approaches in the ICU. Without solid evidence, nearly half of the patients in a recent report were treated with antiviral agents.[5]

<u>Anti-viral agents</u>

There is presently no conclusive evidence that currently available anti-viral agents have efficacy against COVID-19. Furthermore, safety of these agents has not been established in

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COVID-19 patients. In fact, a recently published study of lopinavir-ritonavir compared with standard care, showed that combination therapy had no therapeutic advantage over supplemental oxygen, non-invasive or invasive ventilation, antibiotics, vasopressors, renal-replacement therapy and extracorporeal membrane oxygenation that constituted the standard care arm of the study.[17] The study randomized 199 patients 1:1 in an unblinded manner. The absence of efficacy was met with a nearly two-fold higher incidence of grade 3-4 adverse events (AEs) including lymphopenia which occurred in 12.6% of treated patients compared with 5% of patients that received standard care. In addition to the absence of evidence of efficacy, when contemplating unproven, anecdotal therapies, we urge clinicians to consider the risk of AEs that could further compromise critically ill patients.

In the US, remdesivir (which is not commercially available) was given to the country's first patients with SARS-CoV-2 pneumonia under compassionate use.[18] The activity of remdesivir against COVID-19 has been demonstrated in pre-clinical animal models[19] but its efficacy and safety in humans is still under investigation. There are several ongoing trials of remdesivir in both the US and China. These studies will include both mild to moderately ill (NCT04252664) and severely ill COVID-19 patients (NCT04257656) as well as an adaptive treatment trial (NCT04280705).[5]

Glucocorticoids

The use of intravenous glucocorticoids is controversial in the treatment of severe COVID-19 pneumonia and ARDS. The WHO does not recommend their routine use in COVID-19 patients.[3] This stems for experience during the SARS Co-V epidemic[9, 20] for which they were commonly used and findings suggest in viral infection, they may be harmful (i.e., delayed viral clearance).[21] However, in the treatment of ARDS there is evidence that steroids reduce the duration of mechanical ventilation[22, 23] and a recent multi-center study of dexamethasone demonstrated a mortality benefit.[23] A detailed discussion of the use of steroids in COVID-19 patients is beyond the scope of this paper. However, in the context of therapeutic decision making, consideration should be given to the efficacy data for steroid use in ARDS, most of which was generated from rigorously conducted clinical trials.

Immunomodulating agents

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Tocilizumab, an interleukin (IL)-6 receptor antagonist (monoclonal antibody), is FDA-approved for the treatment of rheumatoid arthritis and is currently part of several studies listed on clinicaltrials.gov. Its manufacturer, Roche, has received approval from China and the US to conduct a phase III randomized, placebo-controlled, double-blind trial. The cytokine, IL-6, is an inflammatory cytokine that is central to the immune response to infection.[24] In a recent description of the clinical course of hospitalized COVID-19, serum concentrations of IL-6 were elevated in non-survivors compared with survivors (11.0 vs. 6.3 pg/mL; $p < 0.0001$).[25] Interleukin-6 has also been shown to be elevated in patients with ARDS and is considered a candidate biomarker of mortality in these patients.[26] Sarilumab, a subcutaneously administered IL-6 inhibitor also FDA approved for the treatment of rheumatoid arthritis, is also being examined in several studies for intravenous administration for treatment of COVID-19. However, in the absence of safety and efficacy data from randomized control trials, we do not recommend the routine use of these agents.

Interferon-alpha ($\alpha$) has been proposed as a candidate therapeutic for COVID-19 in the National Health Commission of the People's Republic of China for treatment of COVID-19 (version 6).[27] Interferon-$\alpha$ plays a pivotal role in host defense of viral infection and is FDA-approved for the treatment of hepatitis B and a number of different types of cancer. A small open-labeled study of patients with SARS Co-V showed that in combination with glucocorticoids, subcutaneously administered interferon-$\alpha$ reduced the time to improved oxygen saturation and resulted in a more rapid resolution of chest radiographic findings.[28] The recommendation here however, is for the use of inhaled administration of the drug. The rationale for its use may be to target the site of action and to avoid systemic AEs (which can be severe, granulocytopenia has been reported in up to 90% of patients). Presently, to the best of our knowledge, there are no prospective studies of inhaled interferon-$\alpha$ that demonstrate its safety and efficacy and we are not aware of any planned or ongoing COVID-19 studies in the US that will test its safety and efficacy. However, there are a few studies that are utilizing it in combination with standard care or anti-viral agents. Given the potential for serious AEs we do not advise anecdotal use in critically ill patients with COVID-19.

Other therapeutics

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The use of hydroxychloroquine for the treatment of COVID-19 has received a lot of press recently. Chloroquine and hydroxychloroquine are anti-inflammatory drugs that are primarily used to treat uncomplicated malaria and rheumatic diseases but detailed studies of the specific mechanism(s) of action of these drugs have not been conducted[29]; hydroxychloroquine is preferred because of it has a more favorable AE profile than chloroquine. The rationale for the use of hydroxychloroquine seems to be because of its presumed anti-viral action against COVID-19 by changing the glycosylation of the ACE2 receptor, presumably interfering with viral binding and invasion, but evidence for this is from *in vitro* and small observational studies.[30-32] The addition of azithromycin to hydroxychloroquine has been explored, not only for possible bacterial co-infection (although less likely based on current evidence), but for its potential anti-viral action, for which there is also limited evidence.[33] Notably, in the most recent trial of azithromycin combined with hydroxychloroquine in hospitalized patients, which was neither randomized nor blinded, only 20 of the enrolled 26 patients that received hydroxychloroquine (six of whom also received azithromycin) were included in the analysis.[32] The authors reported a hydroxychloroquine-induced reduction in the percentage of patients with positive tests but of the 6 patients that were not included in the analysis, three were transferred to the ICU and one patient died. Therefore, given the results of this study and known risk of azithromycin alone or in combination with hydroxychloroquine (both are associated with QT prolongation), additional data are needed prior to any recommendation to utilize azithromycin as part of a treatment regimen for COVID-19.

Ongoing clinical trials and other considerations

As of Friday, March 20, 2020 there were 125 studies related to COVID-19 listed on the clinicaltrials.gov website. Of these, 48 were applicable to critically ill patients and most appear to be open-label, non-randomized studies. In the US, a number of studies are either close to being or are already underway. We would like to emphasize that at the time of publication of this paper, there are no FDA approved treatments for severe or critical COVID-19 that have undergone rigorous scientific testing. Nevertheless, despite little evidence for efficacy and safety, recommendations for specific pharmacotherapy are making their way into guidance documents (e.g., Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused

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by COVID-19 issued by the National Health Commission of the People's Republic of China for treatment of COVID-19)[27] and hydroxychloroquine and chloroquine have received emergency use authorization from the FDA. Simultaneously, there are already reports of harm from these treatments.

We strongly caution the use of unproven, anecdotal therapies in critically ill COVID-19 patients, particularly in those with co-morbidities in which the risk of AEs and possibly inadvertent drug interactions can occur (see http://www.covid19-druginteractions.org/ for a comprehensive list). It is important that we avoid the missteps of HIV-AIDS and cyclosporine[34, 35] or trichosanthin.[36, 37] Furthermore, overuse of such medications can lead to drug shortages for either completion of trials or for patients that genuinely need them. We urge providers to base therapeutic decision making on sound scientific evidence.

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Table: Classification of COVID-19 Severity[3]

| Classification | Criteria | Estimated Percentage of COVID-19 Positive Patients |
|---|---|---|
| Mild | No pneumonia; uncomplicated upper respiratory infection | 80% |
| Moderate | Mild pneumonia | |
| Severe | Severe pneumonia with respiratory rate >30 bpm, severe respiratory distress or $SpO_2$ < 90% on room air | 13.8% |
| Critical | ARDS*; severe cardiac complications[+]; sepsis or septic shock | 6.1% |

$SpO_2$: peripheral capillary oxygen saturation

*Acute respiratory distress syndrome per the Berlin definition[38]

[+]Severe cardiac complications include ischemia, cardiac arrest, acute heart failure, and arrhythmias

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