COVID-19 Pharmacotherapy Treatment Guidance

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Overview

The World Health Organization (WHO) states there is no current evidence to recommend any specific anti-COVID-19 supportive or antiviral treatment for patients with confirmed COVID-19. There are many ongoing clinical trials and data is emerging frequently. Use of investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.

Antiviral Treatment Algorithm

- This information is provided to share information to help guide treatment conversations. State mandates, medication availability/shortages, and access to Infectious Disease resources may impact some of these recommendations at given sites. As additional information becomes available, this information will be updated accordingly.
- Prophylaxis
  - Evidence does not support use of Hydroxychloroquine, or any other agent, for prophylaxis of CoVID-19. Use of Hydroxychloroquine for prophylaxis will rapidly deplete the limited supply and lead to the inability to treat the acutely ill. Supply of these medications will only be used for treatment.
- Treatment
  - COVID-19 positive, or suspect patients, should be approved by Infectious Diseases and/or a Critical Care Provider/Intensivist at sites with these services prior to dispensing
  - Due to demand, intermittent shortages of these agents can be expected

Patient Subset	Antiviral Therapy	Comments
MILD SYMPTOMS **1. Confirmed COVID-19** **2. No radiographic evidence of pneumonia**	None Clinical observation & supportive care	
MODERATE SYMPTOMS **1. Confirmed COVID** **2. Plus any of the following:** a. Radiographic evidence of pneumonia b. Hypoxia requiring supplemental O_2 with at least 50% FiO2 (if not on oxygen at baseline) c. O_2Saturation less than 90% or Pa02/Fi02 <300 d. Immunosuppression on any supplemental oxygen or with pneumonia on X-ray or CT	Supportive Care <AND > Hydroxychloroquine 400mg PO twice daily x 2 doses then 200 mg PO twice daily x at least 4 days, based on clinical response (may consider substitution with Chloroquine 500 mg PO twice daily x 10 days)	• Supportive care is standard therapy • Hydroxychloroquine tablets can be crushed. If a film coating is present, it should be removed first. An extemporaneously prepared suspension may be made with tablets. • Hydroxychloroquine drug interactions: High risk of drug interactions exists with any of the suggested therapies for management. Please refer to http://www.covid19-druginteractions.org/* for table of drug interactions, especially those receiving immunosuppressive therapy. Common DDI include Azithromycin, Amiodarone, Digoxin, and Antacids. Hydroxychloroquine Warnings: • Cardiovascular: Hydroxychloroquine may either cause direct myocardial toxicity or exacerbate underlying myocardial dysfunction; monitor for heart block, QT prolongation. Patients with higher risk for QTc prolongation (elderly (>75yo), female, bradycardia,

		hypokalemia, hypomagnesemia, heart disease, h/o QTc prolongation) should be on continuous cardiac monitoring and have electrolytes replaced daily to the higher end of normal (K>3.8, Mg>1.8) Considerations in pregnancy: • Hydroxychloroquine: limited human data: probably compatible. Has been used routinely in pregnant/nursing RA patients. Use of higher doses probably represents an increased risk to the fetus, magnitude of risk is unknown. • Nursing mothers – excreted in breast milk and some sources recommend caution • Potential risk of hemolytic anemia in patients with G6PD deficiency. N published studies quantify this potential risk. Consider testing for G6PD deficiency. Other hydroxychloroquine tolerability/adverse effects: • Dermatologic: Erythroderma, skin pigmentation disorder • Endocrine: Hypoglycemia (Severe) • Hematologic: Agranulocytosis, Aplastic anemia, Thrombocytopenia • Musculoskeletal: Myopathy/muscle weakness • Psychiatric: Anxiety, hallucination • Respiratory: Bronchospasm has been reported • Ocular: retinal disorder only with prolonged use of greater than 5 years (7.5%) Monitoring/Labs: CBC, ECG, BMP
SEVERE SYMPTOMS **1. Confirmed COVID plus Mechanical Ventilation**	Supportive Care <AND> Consider Hydroxychloroquine 400mg PO twice daily x 2 doses then 200 mg PO twice daily x at least 4 days, based on clinical response (may consider substitution with Chloroquine 500 mg PO twice daily x 10 days) <+/-> Azithromycin 500mg PO x 1 then 250mg PO daily x 4 days (*must monitor QTc) <AND> Consider remdesivir (investigational drug) compassionate use request if inclusion/exclusion criteria met	• The addition of azithromycin to hydroxychloroquine has very limited evidence of benefit. Increased risk of cardiovascular adverse effects should be considered before initiation. • Remdesivir requires obtaining an E-IND (Emergency Investigational New Drug Application) for expanded use (compassionate use) which can take UP TO 72 HOURS. o Current information on remdesivir patient criteria can be found at https://rdvcu.gilead.com/. o Information on the process for obtaining remdesivir and a patient information/ consent form can be found at http://www.trinity-health.org/covid19-pulse o FDA/IRB approval and informed consent necessary if approved • Remdesivir is a prodrug metabolized via CYP3A4, avoid concomitant CYP3A4 inhibitors if possible.* • Remdesivir has been generally well tolerated in preclinical and clinical studies to date. Self-limiting, reversible hepatotoxicity has been observed, which resolved after therapy cessation. Nephrotoxicity has been observed in preclinical studies.

Other Pharmacotherapy Considerations

Other Antivirals

- A recent trial of adults hospitalized with severe COVID-19 treated with Lopinavir–Ritonavir (Kaletra®) has shown no benefit over supportive care and is not recommended (Cao et al.). Darunavir/cobisistat activity against COVID-19 has not been confirmed, activity is extrapolated from other coronaviruses (SARS/MERS).
- Oseltamivir and other neuraminidase inhibitors do not appear to have activity against other coronaviruses (SARS), and should be reserved for treatment of influenza.

Interleulin-6 Inhibitors

Some emerging evidence suggests that some patients may respond to COVID-19 with an exuberant "cytokine storm" reaction. Limited data is available for use of IL-6 receptor antagonists for treatment of COVID. A clinical trial is underway to evaluate the benefit of the IL-6 antagonist Sarilumab (Kevzara®) in COVID patients. A single retrospective review of 20 COVID patients, with known baseline elevated IL-6 levels, treated with a combination of supportive care along with lopinavir, methylprednisolone, and the IL-6 inhibitor Tocilizumab (Actemra®) which showed promise. Most centers do not have IL-6 levels readily available, making the application of this small report problematic. Due to limited data at this time routine use is not recommended. In consultation with an Infectious Disease or critical care physician, off – label adjunctive tocilizumab could be considered for a patient that meets all of the following criteria: Site cannot enroll patient into sarilumab clinical trial, mechanically ventilated patients with severe disease refractory to supportive care and antiviral treatment, and presence of elevated levels of inflammatory markers. More readily available inflammatory markers than IL-6 levels that could be used for evaluation include CRP levels (> 60 mg/L) or Ferritin levels (>300 mcg/L).

Corticosteroids:

- The World health organization does not recommend the routine use of systemic corticosteroids for treatment of viral pneumonia outside of clinical trials due to prior studies in patients with closely related viruses (SARS-CoV and MERS-CoV) showing a lack of effectiveness and possible harm. Clinicians considering corticosteroids for a patient with COVID-19 and with sepsis must balance the potential small reduction in mortality with the potential for prolonged shedding of coronavirus.
- Society of Critical Care Medicine recommendation: For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid therapy (weak recommendation, low quality evidence).
    - Remark: A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.
- CDC guidelines also do not recommend corticosteroid therapy unless indicated for other evidence-based reasons (e.g. COPD exacerbation or septic shock).
- Based on above recommendations, corticosteroids should be considered only for select patients with COVID-19 related refractory shock. If used, treatment should be given at doses of no more than hydrocortisone 200 mg per day for a duration of no longer than 1 week without tapering.

ACE Inhibitors and ARBs

There is interest in the potential role of ACE-inhibitors and angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. However, current guidance from cardiology organizations (i.e. ACC/AHA/HFSA) state that there is not enough evidence to recommend for or against these medications in the setting of the COVID-19 pandemic.

- The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease.
- In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

NSAIDS

The FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs) could worsen coronavirus disease (COVID-19). However, there is no scientific evidence to support these claims to date. The agency is investigating this issue and currently does not have any specific recommendations to withhold NSAID therapy in these patients. The European Medicines Agency has also issued guidance that there is not enough data to recommend avoiding NSAIDS in COVID patients.

Respiratory Treatments

Inhaled medications can be delivered either by Metered Dose Inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive or patients suspected to have COVID, the use of MDIs is preferred when / if available. Please refer to the " Patients and Inhaled Respiratory Medications - Changes to Current Processes" document at http://www.trinity-health.org/covid19-pulse.

Other Care Considerations

Patient positioning

Colleagues from Providence St. Joseph, who cared for the first US patient, report that placing patients with shortness of breath in the prone position was helpful in delaying and even avoiding the placement of COVID-19 patients on mechanical ventilation.

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