COVID-19 Pharmacotherapy Treatment Guidance

May 6, 2020

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.

Therapeutics

- 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.
- 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
  - Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available at the ASHP COVID resource center: ASHP COVID Evidence Assessment
  - Given the scarcity of data, the IDSA panel expressed the overarching goal that patients be recruited into ongoing trials whenever possible to provide much needed evidence on the efficacy and safety of various therapies for COVID-19 (IDSA COVID-19 Guidelines).

Patient Subset	Therapeutics	Comments
NON-SEVERE DISEASE **1.** Confirmed or suspected COVID-19	**Clinical observation & supportive care**	• Supportive care is standard therapy • Hydroxychloroquine is not recommended for outpatient use. The FDA emergency approval for use (EUA) applies to use of hydroxychloroquine only in hospitalized patients under careful heart monitoring.
SEVERE DISEASE **1. Confirmed or suspected COVID plus of the following:** a. Oxygen saturation (SpO2) ≤ 94% on room air b. Requiring supplemental oxygen c. Requiring mechanical ventilation d. Requiring extracorporeal membrane oxygenation (ECMO)	**Supportive Care** **< AND >** **Remdesivir, if available (see comments section)** Insufficient evidence to recommend for or against: Hydroxychloroquine* 400mg PO twice daily x 2 doses then 200 mg PO twice daily x 4 days. (Duration up to 7 days may be considered based on clinical response)	• For more information on Remdesivir availability – please see "**Remdesivir Availability FAQ**" on the Trinity Health COVID site • **See "Use of Remdesivir" section below for information on FDA emergency approval for use (EUA), adverse effect profile, drug interactions, and monitoring.** • Prior to Remdesivir therapy, all patients must have a baseline eGFR and hepatic function testing, and must be provided information consistent with the Remdesivir Fact Sheet for Patients And Parent/Caregivers. • Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline. Daily monitoring of hepatic function is required during therapy. • **If used, please see "Use of Hydroxychloroquine" section below for information on FDA emergency approval for use (EUA), adverse effect profile, drug interactions, and monitoring.** • Prior to therapy, obtain a baseline electrocardiogram to assess for QT interval prolongation and other

		abnormalities. Baseline evaluation of renal and hepatic function is recommended. • Prior to prescribing/dispensing the patient or caregiver should be given the Hydroxychloroquine Fact Sheet for Patients and Parents/Caregivers

Use of Remdesivir: Patient Selection, Dosing, and Monitoring

- The FDA has provided an EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR for treatment of COVID-19 in adults and children hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).
- Prior to treatment the parent/caregiver should be provided information consistent with the "Fact Sheet for Patients And Parent/Caregivers Emergency Use Authorization (EUA) Of Remdesivir For Coronavirus Disease 2019 (COVID-19)"
    - The following information must be documented in the patient's medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to receiving remdesivir, and informed that remdesivir is an unapproved drug that is authorized for use under EUA.
- **Contraindications and Precautions:**
    - Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline
    - Remdesivir is not recommended in adults and pediatric patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk.
- **Dosing**

Adult Dosing	**Treatment of hospitalized COVID-19 patients (EUA, HCP factsheet)** • Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1 • Maintenance: 100 mg IV (over 30-120 minutes) once daily for a total duration of 5-10 days o 5-day dosing recommended in patients NOT requiring invasive mechanical ventilation and/or ECMO, with option to extend treatment for an additional 5 days o 10-day dosing recommended in patients requiring invasive mechanical ventilation and/or ECMO
Pediatric Dosing	**Treatment of hospitalized COVID-19 patients (EUA, HCP factsheet)** *Patients weighing 3.5 to less than 40 kg* • Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1 • Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5-10 days o 5-day dosing recommended in patients NOT requiring invasive mechanical ventilation and/or ECMO, with option to extend treatment for an additional 5 days o 10-day dosing recommended in patients requiring invasive mechanical ventilation and/or ECMO *Patients weighing ≥40 kg* • See adult dosing
Dose Adjustments	Renal: none for mild/moderate impairment; should NOT be given to severe impairment (eGFR <30, or full-term neonates with serum creatinine ≥1 mg/dL) or patients on hemodialysis unless benefit outweighs risk Hepatic: no data, likely do not use in severe impairment; Do not use in patients with AST/ALT elevations >5x the upper limit of normal

- **Monitoring:**
    - Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving (should discontinue therapy for ALT ≥5x ULN and may be restarted when levels decrease <5x ULN)

- All patients should have eGFR determined before dosing. Remdesivir is not recommended in adults and pediatric patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk.
- The following laboratory tests should be performed daily while receiving remdesivir: serum chemistries, hematology, ALT, AST, bilirubin, and alkaline phosphatase; renal function tests (creatinine and creatinine clearance).
- If a serious and unexpected adverse event occurs and appears to be associated with the use of remdesivir, the prescribing health care provider and/or the provider's designee should complete and submit a MedWatch form to FDA as instructed in the Health Care Provider factsheet

- **Adverse reactions**
- An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.
- Other adverse effects with incidence ≥10%
  - Constipation (14%) [15% in placebo group]; Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)
- Infusion-related reactions have been observed during, and/or have been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.
- **Considerations in pregnancy**
- Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. No adverse embryo-fetal evens seen in pregnant rats and rabbits, insufficient data in humans; only use if benefit exceeds the potential risk to the mother and fetus.

Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring

- The FDA has provided an EMERGENCY USE AUTHORIZATION (EUA) of hydroxychloroquine for:
  - Treatment of adults and adolescents who weigh 50 kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible. The EUA applies to use of hydroxychloroquine only in hospitalized patients under careful heart monitoring.
- The following information must be documented in the patient's medical record. The patient/caregiver has been:
  - Given the "Emergency Use Authorization (EUA) of Hydroxychloroquine Sulfate Fact Sheet for Patients and Parent/Caregivers"
  - Informed of alternatives to receiving authorized hydroxychloroquine, and
  - Informed that hydroxychloroquine is an approved drug authorized for the unapproved indication by the EUA
- **Contraindications:**
  - Hydroxychloroquine sulfate is contraindicated in the presence of retinal or visual field changes of any etiology and in patients with known hypersensitivity to 4-aminoquinoline compounds.
  - Hydroxychloroquine sulfate should not be used in patients with a prolonged QT interval at baseline or at increased risk for arrythmia[#] .
- **Dosing:** The optimal dosing and duration of treatment for COVID-19 is unknown. See table for the suggested dose from the FDA EUA. 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.
- **Monitoring:**
  - Prior to treatment: Baseline evaluation of renal and hepatic function is recommended. A baseline electrocardiogram should be obtained to assess for QT interval prolongation and other abnormalities.
  - Monitoring for QT Prolongation and Management:
  - Prior to therapy, obtain a baseline electrocardiogram (ECG) to assess for QT interval prolongation and other abnormalities. Use telemetry whenever possible instead of repeat or daily ECGs, for re-assessment.

a) If baseline QTc is less than 470ms for a male or 480ms for female, start therapy and utilize telemetry whenever possible to recheck QTc in 24 hours.
b) If baseline QTc is 470-500ms, correct any electrolyte imbalances and evaluate medication profile for other QT prolonging drugs that can be discontinued. Begin therapy and recheck QTc at 2-4 hours post dose, then in 24 hours, and 48 hours.
c) If baseline QTc > 500 correct any electrolyte imbalances and evaluate medication profile for other QTc prolonging drugs that can be discontinued. If therapy is started, document the risk is outweighed by the benefit outweighs the risk of therapy.
d) If at any point during therapy the QTc increases by 60ms or more or QTc is above 500ms, drug therapy should be reevaluated for benefits and risk.

- The prescribing health care provider, or designee, is responsible for reporting medication errors and serious adverse events associated with hydroxychloroquine treatment within 7 days.
  - Serious adverse events are defined as: death; a life-threatening adverse event; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; a congenital anomaly/birth defect; a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

- **Adverse Effects/ Hydroxychloroquine Warnings#:**
  - Cardiovascular: QT prolongation and cardiac toxicity (see monitoring). Hydroxychloroquine may either cause direct myocardial toxicity or exacerbate underlying myocardial dysfunction.
    - Use with caution in patients with cardiac disease and/or with higher risk for QT prolongation: history of ventricular arrhythmias, bradycardia, uncorrected potassium or magnesium imbalance, elderly (age > 75 y.o.), female, and during concomitant administration with QT interval prolonging medications (including azithromycin). Myocarditis, pericarditis, and cardiomyopathy may increase risk for arrythmia. Monitor for cardiac injury.
  - Hypoglycemia: Hydroxychloroquine sulfate has been reported to decrease insulin clearance and resistance. Loss of consciousness in patients with or without the use of antidiabetic medications has been reported.
  - Hematologic effects: Hemolysis in G6PD deficient patients, pancytopenia, aplastic anemia and neutropenia have been reported.
  - Hepatic impairment: Since hydroxychloroquine sulfate is known to concentrate in the liver, it should be used with caution in patients with hepatitis, hepatic disease, alcoholism or in conjunction with known hepatotoxic drugs.
  - Renal impairment: Hydroxychloroquine sulfate is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Some experts recommend a dose reduction of 50% for GFR < 10 mL/minute, hemodialysis, or peritoneal dialysis; no dose reduction is recommended if GFR > 10 mL/minute.
  - Central nervous system effects: Hydroxychloroquine sulfate may increase the risk of convulsions in patients with a history of seizures. Acute extrapyramidal disorders may occur with hydroxychloroquine sulfate. Psychosis, delirium, agitation, confusion, suicidal behavior, and hallucinations may occur with hydroxychloroquine sulfate.
  - Retinopathy: Retinal damage has been observed in some patients receiving long-term treatment with hydroxychloroquine sulfate.
- **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 for inpatients with Hydroxychloroquine may include Antacids, Antiepileptics, Azithromycin, Amiodarone, Cyclosporine, Digoxin, and Tamoxifen.
- **Considerations in pregnancy:**

  The individual benefit-risk balance should be reviewed before prescribing hydroxychloroquine sulfate in pregnant women. Limited human data although therapy 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.

- In humans, at recommended doses for prophylaxis and treatment of malaria, observational studies as well as a meta-analysis, including a small number of prospective studies with hydroxychloroquine sulfate exposure during pregnancy, have shown no increase in the rate of birth defects or spontaneous abortions. In animal studies, embryo-fetal developmental toxicity was shown at doses approximately 3 to 16 times the maximum recommended therapeutic dose based on a body surface area comparison. Preclinical data showed a potential risk of genotoxicity in some test systems.
- Nursing mothers – excreted in breast milk and some sources recommend caution.

- **Discharging Patients on Hydroxychloroquine**
  - If otherwise ready for discharge, patients should not be held in the hospital exclusively for the purpose of hydroxychloroquine administration and related arrhythmia monitoring.
  - The course of hydroxychloroquine may be completed upon discharge, at the discretion of the provider, based on risk and benefit if the QTc intervals remained well within normal range and had no concerning arrhythmias on telemetry during therapy throughout admission. Review of discharge medications should be performed to ensure any additional home medications are considered for drug-drug interactions.

Azithromycin

- Evidence to support the combination of hydroxychloroquine with azithromycin improves clinical outcomes for treatment of COVID-19 is lacking.[1,6] However, the combination of these drugs is known to increase the likelihood of QTc prolongation which can lead to life-threatening arrhythmias and sudden cardiac death[7-9].
- Because of the potential for toxicity, routine use of this combination for inpatient treatment of COVID-19 in the absence of secondary bacterial infection is not recommended. If used, cardiac monitoring as outlined in the Cardiovascular section above, should be followed.
- For outpatients the use of antimicrobial regimens, including azithromycin, are only encouraged under approved conditions for treatment of bacterial pneumonia. Routine use in COVID is not recommended.

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. Very 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®) from China showed promise. There is currently no data available for use of Sarilumab. 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 outside of a clinical trial setting is not recommended. In consultation with an Infectious Disease and/or critical care physician, off – label adjunctive IL-6 inhibitor use may only be considered for a patient that meets all of the following criteria: Site cannot enroll patient into an

IL-6 inhibitor 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.
- CDC guidelines also do not recommend corticosteroid therapy unless indicated for other evidence-based reasons (e.g. COPD exacerbation or septic shock).
- Society of Critical Care Medicine recommendations:
    - In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids (weak recommendation, low quality evidence).
    - In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence). The ideal dose of corticosteroid for this indication is unknown.
    - 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). Based on above recommendations, corticosteroids should be considered only for select patients with COVID-19 related refractory shock.
        - Based on SCCM recommendations, if corticosteroids are used for refractory shock, 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.

Thromboprophylaxis Considerations: Inpatient and Post-discharge

- Please see guidance document on thromboprophylaxis considerations for COVID positive patients: http://www.trinity-health.org/workfiles/covid-19/post-discharge-thromboprophylaxis-considerations.pdf

Other Care Considerations

Patient positioning

- For non-intubated patients, please see the "Prone Positioning for the Non-intubated Patient" reference on the Trinity Health COVID site.
- For intubated patients, the American Thoracic Society suggests prone ventilation for patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS). Refractory hypoxemia refers to an SpO2 consistently less than 90% despite maximal ventilator interventions to increase the SpO2.

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Version History

Version Date	Revisions Made
3/30/2020	Updated Remdesivir compassionate use information.
4/4/2020	Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in 'Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring" section
4/14/2020	Updated information on Remdesivir access. Removal of azithromycin from recommendations. Added ASHP evidence summary reference. Added IDSA guidelines reference. Updated patient positioning/prone references.
4/28/2020	Added reference to FDA Drug Safety Communication that cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Added information on Discharging Patients on Hydroxychloroquine
05/4/2020	Added outpatient pharmacotherapy guidance.
05/6/2020	Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.