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**
  o Evidence does not support use of Hydroxychloroquine, or any other agent, for prophylaxis of COVID-19.
- **Treatment**
  o 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
  o Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available at the ASHP COVID resource center: [ASHP COVID Evidence Assessment](#)
  o 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](#)).

<table>
<thead>
<tr>
<th>Patient Subset</th>
<th>Therapeutics</th>
<th>Comments</th>
</tr>
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</table>
| **NON-SEVERE DISEASE**  
Confirmed or suspected COVID-19 | Clinical observation & supportive care | • Supportive care is standard therapy  
• Hydroxychloroquine is NOT recommended |
| **SEVERE DISEASE**  
Confirmed or suspected COVID plus of the following:  
a. Requiring supplemental oxygen  
b. Oxygen saturation (SpO2) ≤ 94% on room air  
c. Requiring mechanical ventilation  
d. Requiring extracorporeal membrane oxygenation (ECMO) | Supportive Care < AND > Remdesivir, if available (see comments section) | Remdesivir Comments  
• For information on availability – please see the Remdesivir Availability document on the Trinity Health COVID site  
• See "Use of Remdesivir" section below for information on FDA emergency approval for use (EUA), contraindications, 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.  
• In the setting of limited Remdesivir supply, consult local Chief Medical Officer  

Hydroxychloroquine Comments  
Based on emerging evidence showing a lack of efficacy and increased risk of adverse effects, use of Hydroxychloroquine for treatment of COVID-19 is NO LONGER recommended as risks outweigh benefits.
Use of Remdesivir: Patient Selection, Dosing, and Monitoring

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (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). The full EUA from FDA is available here: EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR

- 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
- Accumulation of the IV vehicle sulfobutyl-ether beta-cyclodextrin sodium (SBECD) occurs in patients with renal impairment. Use with caution in adults and pediatric patients with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥ 1 mg/dL.

Considerations in pregnancy

- No adverse embryo-fetal events seen in animal models, however there is insufficient data in humans
- Remdesivir should be used only if benefit exceeds the potential risk to the mother and fetus.
- Pregnant patients with significant clinical manifestations may qualify for the emergency use program - please see the Remdesivir Availability document on the Trinity Health COVID site

Dosing per FDA EUA Document

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (EUA, Healthcare Provider Factsheet)</th>
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<tbody>
<tr>
<td></td>
<td>• Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1</td>
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<tr>
<td></td>
<td>• Maintenance: 100 mg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Pediatric Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (EUA, Healthcare Provider Factsheet)</th>
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</thead>
<tbody>
<tr>
<td>Patients weighing 3.5 to less than 40 kg</td>
<td>• Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1</td>
</tr>
<tr>
<td></td>
<td>• Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
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<tr>
<td>Patients weighing ≥40 kg</td>
<td>• See adult dosing</td>
</tr>
</tbody>
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Duration

- The optimal duration of Remdesivir treatment for COVID-19 is unknown. Shorter courses (less than 10 days) may be appropriate based on clinical response.
- The FDA EUA document provides the following duration recommendations:
  - 5-day dosing recommended in patients NOT requiring invasive mechanical ventilation and/or ECMO, with option to extend treatment for an additional 5 days
  - 10-day duration is recommended in patients requiring invasive mechanical ventilation and/or ECMO (consider shorter course as discussed above)
  - Based on clinical experience Trinity recommends a 5 day course, which may be extended to 10 days based on response [see also Goldman J, et al. NEJM, May 27, 2020, and Beigel JH, et al. NEJM, 5/22/2020, under references]

Dose Adjustments

- Renal: No pharmacokinetic data for mild or moderate hepatic impairment.
- Hepatic: No pharmacokinetic data for mild or moderate hepatic 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.

Nursing Considerations

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.

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%)

Hydroxychloroquine

Based on emerging evidence showing a lack of efficacy and increased risk of adverse effects, use of Hydroxychloroquine for treatment of COVID-19 is NO LONGER recommended as risks outweigh benefits. [see also Mehra MR, et al. Lancet, 5/22/2020, under references]

Azithromycin

Evidence to support the combination of hydroxychloroquine with azithromycin improves clinical outcomes for treatment of COVID-19 is lacking. 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.

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).

The triple combination of lopinavir, ritonavir and ribavirin with or without interferon beta-1b, may reduce duration of symptoms among patients who have been admitted to the hospital with COVID-19 based on preliminary data. Use of this triple antiviral regimen, and interferon beta-1b, should only be within the context of a clinical trial.

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: Thromboprophylaxis Considerations in COVID Patients

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.

References:


6. FDA Drug Safety Communication: FDA 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.

8. John R. Giudicessi, MD, PhD; Peter A. Noseworthy, MD; Paul A. Friedman, MD; and Michael J. Ackerman, MD, PhD. Urgent Guidance for Navigating and Circumventing the QTc Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for COVID19. DOI: https://doi.org/10.1016/j.mayocp.2020.03.024


30. Sarilumab (Kevzara®) https://www.regeneron.com/covid19
31. https://www.nature.com/articles/s41467-020-13940-6
39. Use of Remdesivir Provided by the State of Michigan For Treatment of COVID-19 Frequently Asked Questions

Version History

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<thead>
<tr>
<th>Version Date</th>
<th>Revisions Made</th>
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<tbody>
<tr>
<td>3/30/2020</td>
<td>Updated Remdesivir compassionate use information.</td>
</tr>
<tr>
<td>4/4/2020</td>
<td>Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in &quot;Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring&quot; section</td>
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<tr>
<td>Date</td>
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<tr>
<td>4/28/2020</td>
<td>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</td>
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<tr>
<td>05/4/2020</td>
<td>Added outpatient pharmacotherapy guidance.</td>
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<tr>
<td>05/6/2020</td>
<td>Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.</td>
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<tr>
<td>05/13/2020</td>
<td>Recommendation added to limit use of triple antiviral therapy and interferon beta to use in a clinical trial only</td>
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<tr>
<td>5/20/2020</td>
<td>Updated recommendations on use of Remdesivir in renal impairment and duration of therapy. Nursing considerations comment added.</td>
</tr>
<tr>
<td>5/28/2020</td>
<td>Hydroxychloroquine no longer recommended.</td>
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