COVID-19 Inpatient Adult Treatment Guidelines

September 15, 2020

Note: Because COVID-19 is a novel virus, **there is very limited evidence to support effective treatments.** This guideline outlines currently available information and is authorized by the CommonSpirit Health System P&T Committee. Information is changing rapidly, please check for updates frequently. ***Revisions for this version are underlined.***

SARS-CoV-2 (COVID-19) infection based on positive PCR or antigen* and clinical syndrome → Evaluate for clinical trial enrollment, depending on site availability and patient qualifications

Based on currently available information, the best care is supportive care, including:

- **Fluid management.** Conservative fluid strategies should be encouraged, including aggressive conversion to PO, eliminating unnecessary intravenous medications, and concentration of IV fluids when feasible.
- **Prone positioning.** Consider prone positioning early in treatment course for patients with mild to moderate hypoxia.
- **Anticoagulation.** Systemic anticoagulation may be associated with improved outcomes among patients hospitalized with COVID-19.[1]
  - All patients with COVID should at least be on prophylactic dose of enoxaparin (preferred) or SQ heparin unless contraindicated.
  - In critically ill patients with COVID-19, the CHEST guidelines (published 6/23/2020) suggest current standard dose anticoagulant thromboprophylaxis over intermediate (LMWH BID or increased weight-based dosing) or full treatment dosing, per existing guidelines.[2] At the time of writing there were no randomized trials assessing enhanced anticoagulation compared to standard anticoagulation in patients with COVID-19.
  - Anecdotally, it has been found that some patients may need anticoagulation beyond standard prophylactic dosing due to a hypercoagulable state (e.g., elevated D-dimer). Some institutions are using augmented anticoagulation (e.g. enoxaparin SQ 40 mg BID) to treat these patients. In ICU patients, some institution are using full anticoagulation based on patient presentation. Prophylactic and therapeutic anticoagulation has been shown to lower mortality when compared to no anticoagulation.[3] (ref)
  - All patients on therapeutic anticoagulation at home (e.g., atrial fibrillation) should remain on therapeutic anticoagulation
  - Utilize therapeutic dosing if a thromboembolism is suspected.
  - Consider renal function on choice and dosing of anticoagulants.
  - Mechanical thromboprophylaxis should be used when pharmacological thromboprophylaxis is contraindicated.[3]
  - Monitoring
    - Consider Xa monitoring in patients that may be overweight (>120 kg), underweight or fluctuating renal function.
    - Consider TEG monitoring in critically ill patients or patients with evidence of thrombosis.
    - If fibrinogen <0.5 g/L or if platelet count less than 25 x 10^9/L, consider holding anticoagulation.
  - At hospital discharge, data is sparse for appropriate duration and intensity of anticoagulation requirements in patients with COVID. If a patient requires anticoagulation while inpatient, evaluate if continued anticoagulation would be appropriate.
- **Steroids.**
  - Based on the preliminary results of the RECOVERY trial[5]:
    - The COVID-19 Treatment Guidelines Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen.[6] Patients with severe ARDS may require higher steroid doses.[7]
    - Oral dexamethasone is preferred over IV if a patient can take oral medications.
    - The NIH Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI).[6]
  - If needed, equivalent glucocorticoid dose may be substituted if dexamethasone unavailable . Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.[6,8]
  - Consider screening patients at high risk for infections exacerbated by corticosteroids (e.g., *Stongyloides*, TB). Treat as indicated. Patients from tropical areas are at risk of *Strongyloides*.[9]

Remdesivir (continued on following pages)[10]

- **Availability**
  - Supply of free, allocated product at state departments of health may be limited. Now available from AmerisourceBergen with a cost of $3,120 per 5 day treatment course. Health departments will determine how much remdesivir hospitals within their respective jurisdictions may purchase based on the state allocation.
  - 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 to treat all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, irrespective of their severity of disease.[11]

*Clinical diagnosis and strong epidemiological links may be considered. Supportive treatment can be considered in absence of testing confirmation.

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Remdesivir (continued)

- **Evidence**
  - Preliminary data suggests the patients with greatest benefit are those on supplemental oxygen and not intubated at the time of initiation.[12]
  - A comparative pre-planned analysis was released via press release (not yet peer reviewed or published). It included patients treated in the Phase 3 SIMPLE-Severe study and a separate real-world retrospective cohort who received standard of care treatment in the same time period as the SIMPLE-Severe study. While mortality data was provided, the scientific merit of this study design and how well the baseline characteristic were matched is unclear. More information is needed for this data to change practice.[13]
- **Dosing**
  - Due to the severely limited supply of remdesivir and recent data from Gilead, treatment is limited to a 5 day treatment course.[14]
  - Adults and children weighing ≥ 40 kg[10]
    - Day 1: Single loading dose of 200 mg infused IV over 30 to 120 minutes
    - Days 2 to 5: Once daily maintenance doses of 100 mg infused IV over 30 to 120 minutes for 4 days
  - Pediatric patients weighing between 3.5 kg and <40 kg[10]
    - Day 1: Single loading dose of 5 mg/kg infused IV over 30 to 120 minutes
    - Days 2 to 5: Once daily maintenance doses of 2.5 mg/kg infused IV over 30 to 120 minutes for 4 days.
- **Use Criteria** (based on currently available information)
  - **Inclusion Criteria (must meet all)**
    - COVID + or strong epidemiologic link
    - Requiring at least 2 liters of oxygen to maintain O_2 Sat of 92%
      - Patient must be on oxygenation orders to maintain O_2 Sat of 92% that includes orders to titrate down oxygen requirements
    - Hospitalized for COVID for no more than 10 days. Within the clinical trials, there was an average symptom onset of 9-12 days. Consider timing of symptom onset when determining appropriateness of therapy initiation. In general, starting treatment earlier is better.
  - **Exclusion Criteria** (at the time of remdesivir initiation).
    - Consider excluding patients with COVID-19 who require noninvasive and invasive mechanical ventilation, or ECMO. The NIH COVID-19 Treatment Guidelines Panel cannot make a recommendation either for or against starting remdesivir in this population.[6] The study published by the NIAID did not show that remdesivir benefited patients on mechanical ventilation or ECMO, either statistically or trending: recovery rate (CI 0.95 (0.64-1.42)) or mortality (hazard ratio/CI 1.06 (0.59 1.92)).[11]
    - ALT > 5x upper limit of normal (must document liver enzymes prior to approval process being done)
    - Consider short-term life expectancy when appropriate (e.g., advanced cardiovascular, pulmonary, or liver disease or 50% chance of mortality within 1 year)
  - **COVID-19 information is rapidly changing and criteria will be updated weekly, if needed.**
  - Recommendation for prioritizing limited supplies of remdesivir :
    - Because remdesivir supplies are limited, the NIH Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on noninvasive ventilation, mechanical ventilation, or ECMO.[6]
    - Hospitals should utilize their local policy and procedures to prioritize the allocated remdesivir.
  - For patients with COVID-19 who are on supplemental oxygen but who do not require high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the NIH Panel recommends using remdesivir for 5 days or until hospital discharge, whichever comes first.[6]
  - If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high -flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the NIH Panel recommends that the course of remdesivir be completed.[6]
  - Facilities may use more restrictive criteria if the clinical need arises.
- **Adverse Reactions and Monitoring**
  - Health care providers must submit a report on all medication errors and ALL SERIOUS ADVERSE EVENTS related to remdesivir.[10]
  - Empiric dosing may be considered pending laboratory confirmation of SARS-CoV-2 infection.
  - Renal function should be tested prior to starting remdesivir. No dose adjustments are needed if eGFR is ≥ 30 ml/min. Remdesivir should be used with caution if eGFR <30 mlmin (benefits must outweigh the risks).
  - Hepatic function testing should be completed prior to starting remdesivir and daily during treatment. It is not known if dosage adjustment is needed in the setting of hepatic impairment. Only use if potential benefit outweighs risk.
    - Do not initiate in patients with ALT ≥ 5 times ULN at baseline
    - Discontinue in patients who develop ALT ≥ 5 times ULN at baseline during treatment with remdesivir. Remdesivir may be restarted when ALT is <5 times ULN
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conj . bilirubin, Alk phos or INR
  - ISMP published an issue (volume 25, issue 18) on September 10, 2020 on reported medication errors with remdesivir. Please see the COVID-19 Daily Bulletin SharePoint site to review this issue. https://dignityhealth.box.com/s/bq0zx7vnh5dr17ueq3g2xfmdzxz893as
- **Additional Information for Healthcare Providers**
  - There are mandatory requirements for remdesivir administration under emergency use authorization. Please see the "Fact Sheet for Healthcare Providers" for details: https://www.gilead.com/-/media/files/pdfs/remdesivir/eua-fact-sheet-for-hcps_01may2020.pdf?la=en&hash=B56F8C441364B7EDA15543F75E8EC88F

Remdesivir (continued)

- **Additional Information for Patients**
  - Communicate to your patient or parent/caregiver information consistent with the "Fact Sheet for Patients and Parents/Caregivers." Provider must document patient or caregiver communication.
    - The "Fact Sheet for Patients and Parents/Caregivers" can be found here: https://www.gilead.com/-/media/files/pdfs/remdesivir%20/eua-fact-sheet-for-patients-and-caregivers.pdf?la=en&hash=18BE014A3864EB86EE43E87917514525
    - The patient or parent/caregiver has the option to accept or refuse remdesivir.
    - The significant known and potential risks and benefits of remdesivir, and the extent to which such risks and benefits are unknown.
    - The patient fact sheet is also available in Spanish
- **Recommended language for remdesivir initiation**
  - I spoke with _(patient/power of attorney)_ to provide information about remdesivir treatment for _(patient)_
  - I offered them the "Patient and Caregiver EUA Remdesivir Fact Sheet" to read and review
  - I stated the drug has been approved by an emergency use authorization (EUA) process and has not fully been FDA reviewed or approved
  - The patient meets the EUA requirements
  - I shared that the drug may cause liver abnormalities and infusion related side effects. Additionally, other side effects are possible but not known as the drug has had limited studies.
  - I discussed there are other potential treatment options that are currently not FDA approved to treat COVID-19.
  - (When applicable) Discussed with patient that pregnancy is not an exclusion for remdesivir treatment, but the drug has not been fully evaluated in pregnant patients
  - Offered opportunity to ask questions and all questions were answered
  - _(patient/power of attorney)_voiced understanding and agreed to proceed with treatment for _(patient)_

COVID Convalescent Plasma (CCP)

- The FDA has issued an Emergency Use Authorization (EUA) to permit the use of COVID-19 convalescent plasma to treat hospitalized patients with COVID-19.[15]
  - **EUA procedures must be followed when administering CCP** including documenting the discussion regarding risks and benefits in the medical record and reporting any adverse reactions.
  - CCP's place in therapy remains unclear at this time. Recommend **only starting within the first 3 days of hospitalization** in patients with co-morbid conditions. After this time, patients likely have their own COVID-19 antibodies.[16]
  - The NIH's COVID-19 Treatment Guidelines Panel states that there are insufficient data to recommend either for or against the use of CCP for the treatment of COVID-19. CCP should not be considered the standard of care for the treatment of patients with COVID-19. Prospective, well-controlled, adequately powered randomized trials are needed to determine whether CCP is effective and safe for the treatment of COVID-19.[6]
  - There are **supply limitations** for obtaining CCP that **both limits the overall availability and potential timing of administration.**
  - The principle data set used for the EUA was from the Mayo Clinic.[17]
    - The partial data set analyzed >35,000 patients without a control group. It spanned a time of continued changing therapies for COVID-19 and changing disease severity at time of entry into the study. Overall crude mortality decreased over time in the study and favored transfusion within the first 3 days.
      - Thirty day mortality in the first month of the trial was 30.4% and 34.6% when treatment was given within 3 days and 4 or more days respectfully.
      - Thirty day mortality in the final month of the trial was 18.4% and 20.2% when treatment was given within 3 days and 4 or more days respectfully.
    - In a subset of 3082 patients adjusted for confounders, a mortality difference was detected overall by difference in antibody titer level. However, the 95% confidence interval overlapped between all three groups (high, medium, and low antibody levels). Medium antibody levels were present in 65% of patients, while low and high levels were in 18% and 17% of patients, respectively.
      - The EUA includes low antibody titer plasma as part of the authorization.
      - Per the EUA, plasma not labeled as "high titer" are to be considered "low titer".
      - Currently, not all blood banks/suppliers of convalescent plasma label the antibody level. The assays to test the antibody levels may or may not be available at this time.
    - Pregnancy was not an exclusion to the Mayo study. An analysis of outcomes in pregnant patients or babies born from these mothers is not currently available. Pregnancy or lactation are not exclusions per the EUA.
  - If available, CCP is supplied through the blood bank and not pharmacy.
  - For additional information, please see the memo entitled, "UPDATE: COVID Convalescent Plasma Emergency Use Authorization," sent on 9/10/2020 and located on the CommonSpirit Health COVID-19 SharePoint sites.
- Recommended language for CCP initiation.
  - I spoke with _(patient/power of attorney)_ to provide information about convalescent plasma for _(patient)_
  - I offered them the "Fact Sheet for Patients and Parents/Caregivers" for COVID-19 convalescent plasma to read and review
  - I stated the therapy has been approved by an emergency use authorization (EUA) process and has not fully been FDA reviewed or approved
  - I shared potential risks from the therapy including transmission of blood borne pathogens such as HIV and hepatitis C, allergic and transfusion related reactions, posttransfusion purpura. Additionally theoretical risks including a phenomenon called antibody-dependent enhancement of infection such as is seen in dengue or attenuation of an immune response that may make patients more susceptible to re-infection

COVID Convalescent Plasma (CCP) (continued)

- I discussed there are other potential treatment options that are currently not FDA approved to treat COVID-19.
- (When applicable) Discussed with patient that pregnancy is not an exclusion for convalescent plasma treatment, but the therapy has not been fully evaluated in pregnant patients
- Offered opportunity to ask questions and all questions were answered
- _(patient/power of attorney)_voiced understanding and agreed to proceed with treatment for _(patient)_

Medication Considerations

- **Aviptadil.** The FDA has granted an Expanded Access Protocol for treatment of Respiratory Failure in COVID-19 with aviptadil, a synthetic form of vasoactive intestinal peptide.[18]
  - It has very limited availability and may not be available at this time.
  - The treatment is available to patients who have exhausted standard therapies and are not eligible for the current Phase 2/3 clinical trial of aviptadil due to confounding medical conditions and specifically makes the treatment available to pregnant women. This is still only investigational but expanded access program is now open.
  - Facilities must apply for Expanded Access and may or may not be accepted. Anecdotally, this is a cumbersome process to undergo. As of today, no CommonSpirit Health facility has obtained this medication.
  - To apply for the aviptadil expanded access program (EAP), a facility would identify a physician sponsor and access the EAP portal at https://www.neurorxpharma.com/. If enrollment is successful, please notify your respective CommonSpirit Health IRB.
- Follow IDSA guidelines for community-acquired pneumonia (CAP) and ventilator-acquired pneumonia (VAP) treatment. Discontinuation of empiric antibiotics is warranted if no bacterial pathogen is isolated and no other source of infection is suspected.
- **Nasal steroids** should be avoid in patients with COVID-19 to minimize staff exposure.
- **NSAIDs**. Persons with COVID-19 who are taking NSAIDs for a co-morbid condition should continue therapy as previously directed by their physician. May use either acetaminophen or NSAIDS as antipyretic strategies.[6] Please note, that not all fevers need to be brought to normothermia.
- **ACE inhibitors/ARBS**. The HFSA, ACC, and AHA recommend continuation of RAAS (renin-angiotensin-aldosterone system) 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.[19] ACEI/ARB were not associated with COVID diagnosis or mortality.[20] Do not use these agents for the sole treatment of COVID-19.[6]
- **Statins**. Continue statins if prescribed for other indications. Do not use these agents for the sole treatment of COVID-19.[6]
- **Paralytics**. When paralytics are indicated, use intermittent dosing strategy as a part of shortage management.
- **Inhaled epoprostenol**. In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, the Surviving Sepsis Campaign suggests a trial of inhaled pulmonary vasodilator (e.g., epoprostenol) as a rescue therapy. If no rapid improvement in oxygenation is observed, the treatment should be tapered off. This is a weak recommendation, with very low quality evidence.[21]
- Consider consulting pharmacy to mitigate drug-drug interactions.
- Align dosage administrations to decrease entry and exit occurrences in patient rooms as much as possible
- Critically evaluate medication routinely to ensure there are no unnecessary therapies ordered
- FDA website available on COVID-19: https://www.fda.gov/health-professionals/coronavirus-disease-2019-covid-19-resources-health-professionals
- Additional medication-related information, please refer to the ASHP website: https://www.ashp.org/Pharmacy-Practice/Resource-Centers/Coronavirus

Medications Without Sufficient Evidence to Recommend for COVID-19 Treatment

Many medications are being trialed anecdotally for treatment of COVID-19. There are continued claims without substantiated clinical efficacy. The below of medications do not have sufficient evidence to recommend in the **absence of another clinical indication.**

- **Treatment with hydroxychloroquine/chloroquine.** While a retrospective , open-label, unblinded, uncontrolled observational study demonstrated some efficacy with hydroxychloroquine,[22] the NIH Panel recommends against the use of chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII).[6] The FDA has withdrawn the EUA for hydroxychloroquine and chloroquine.[21] The NIH and WHO have terminated their randomized, controlled studies assessing hydroxychloroquine due to lack of efficacy.[22] Trials have shown no benefit of hydroxychloroquine for patients with COVID-19.[25-27]
- **Hydroxychloroquine and azithromycin.** Do not use for COVID-19.[6]
- **Prophylaxis with hydroxychloroquine.** Prophylaxis should not be utilized based on results from a large, US based, randomized, placebo controlled trial.[28]
- K**aletra (lopinavir-ritonavir).** In a recent in vivo study, it did not show benefit compared to standard of care.[27] The NIH recommends against the use of this therapy at this time.[6] Additional studies are ongoing, including those with combination therapy.
- **Ribavirin.** There is no evidence to support ribavirin monotherapy as a treatment for COVID-19 at this time.

Medications Without Sufficient Evidence to Recommend for COVID-19 Treatment (continued)

- **Triple therapy with ribavirin, lopinavir-ritonavir and interferon beta-1b** does not have enough evidence to support routine use outside of a clinical trial. The limited data currently available is in patients with mild to moderate disease.[30]
- **IL-6 inhibitors** (e.g., tocilizumab (Actemra)). Use is not recommended at this time outside of a clinical trial.[6] Published data to support use for COVID-19-related ARDS did not show benefit.[31] A trial assessing sarilumab (Kevzara) also showed no benefit.
- **Alteplase.** For a known PE or stroke, use continues to be recommended.
- **Ascorbic acid.** Do not use IV ascorbic acid.
- JAK inhibitors (e.g., baricitinib)
- IL-1 inhibitors (e.g., anakinra) (insufficient data)[6, 32]
- Melatonin
- Pioglitazone
- Zinc
- Thiamine
- Ivermectin[6]
- IVIG. Do not use.
- Interferons. Do not use.
- Famotidine[33]
- Acetazolamide
- Acalabrutinib[34]
- Quercetin
- Colchicine[35]

For non-medication related treatment strategies for critical care patients, please see the CommonSpirit Health Critical Care COVID-19 Clinical Guidelines

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