COVID-19 Treatment Guidelines*

March 9, 2021

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:

- **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 in patients hospitalized with COVID-19.[1]
  - Hospitalized adults with COVID-19 should receive prophylactic dose anticoagulation (AIII).[2]
  - There are currently insufficient data to recommend either for or against the use of thrombolytics or higher than the prophylactic dose of anticoagulation for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.[2]
    - Preliminary data indicate that for patients who are hospitalized, but not on ICU organ-support, therapeutic anticoagulation doses may be better than thromboprophylaxis. However, in patients on ICU-level organ support, full dose anticoagulation did not improve outcomes (but did increase bleeding events).[3]
  - 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. Prophylactic and therapeutic anticoagulation has been shown to lower mortality when compared to no anticoagulation.[4]
- **NIH's recommendations** for pharmacologic management of patients with COVID-19 based on disease severity[2]

Disease Severity	NIH Panel Recommendations
Not hospitalized, mild to moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or monoclonal antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab or casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk for disease progression. Use in patients hospitalized for COVID is not authorized. **Dexamethasone or other corticosteroids** should **not** be used (AIII).
Hospitalized but does not require supplemental oxygen	**Dexamethasone or other corticosteroids** should **not** be used (AIII). There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized and requires supplemental oxygen (Does not require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO)	Use one of the following options: • **Dexamethasone plus remdesivir** (e.g., for patients who require increasing amounts of supplemental oxygen) (BIII) • **Dexamethasone** (e.g., when combination therapy with remdesivir cannot be used or is not available) (BI) • **Remdesivir** (e.g., for patients who require minimal supplemental oxygen) (BIIa)
Hospitalized and requires oxygen delivery through a high-flow device or noninvasive ventilation	Use one of the following options: • **Dexamethasone** (AI) • **Dexamethasone plus remdesivir** (BIII)
Hospitalized and requires invasive mechanical ventilation or ECMO	Dexamethasone (AI)

Rating recommendations: A=strong, B=moderate, C=optional.
Rating evidence: I=One or more randomized trials without major limitations, IIa=Other randomized trials or subgroup analyses of randomized trials, IIB=Non randomized trials or observational cohort studies, III=expert opinion.

*Most data available is for adult patients, extrapolation to children can be considered but with lower certainty of effects and outcomes .
**Clinical diagnosis and strong epidemiological links may be considered. Supportive treatment can be considered in absence of testing confirmation.

CommonSpirit

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Remdesivir (Veklury)[5]

- **Availability**
  - Remdesivir is FDA indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization.
  - For pediatric patients under 12 years of age and weighing 3.5 to less than 40 kg, remdesivir is only available via the Emergency Use Authorization (EUA); it is required that criteria be followed.
- **Evidence and Recommendations**
  - The NIH trial suggests the patients with greatest benefit are those on supplemental oxygen and not intubated at initiation.[6]
    - Current evidence also suggests that remdesivir does not show proven benefit for patients who are mechanically ventilated or on ECMO.
    - The benefit seen is shortened time to recovery (10 days vs. 15 days in placebo). It has not shown an effect on mortality.
  - The SOLIDARITY trial has been released prior to peer review. No mortality benefit was seen, particularly in patients on a ventilator.[7] No improvement was seen for ventilator initiation or length of stay for patients treated with remdesivir.
  - Guidelines: Organizations have reviewed the same data and published conflicting recommendations
    - **The World Health Organization (WHO)** has issued a conditional recommendation against the use of remdesivir in hospitalized patients, regardless of disease severity, as there is currently no evidence that remdesivir improves survival and other outcomes in these patients.[8]
    - **The Infectious Disease Society of America (IDSA)** has issued a conditional recommendation for hospitalized patients with severe COVID-19 to suggest remdesivir over no antiviral treatment (moderate certainty of evidence).[9]
      - In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel makes a conditional recommendation for treatment with five days of remdesivir rather than 10 days of remdesivir (low certainty of evidence).
      - In patients on mechanical ventilation or ECMO, the IDSA panel gives a conditional recommendation that the treatment duration can be 10 days of remdesivir (low certainty of evidence). The benefit from remdesivir for patients on mechanical ventilation or ECMO is unsubstantiated.
  - **Dosing**
    - Data from Gilead indicates that treatment should be limited to a 5 day treatment course or until hospital discharge (whichever comes first).[10]
    - Adults and children weighing ≥ 40 kg[5]
      - 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[5] (use lyophilized powder formulation only)
      - 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)** Facilities may use more restrictive criteria.
  - **Inclusion Criteria (must meet all)**
    - COVID + or strong epidemiologic link
    - Requiring at least 2 liters of oxygen to maintain O_2 Sat of 94%
      - Patient must be on oxygenation orders to maintain O_2 Sat of 94% that includes orders to titrate down oxygen requirements
      - Symptoms of COVID for no more than 10 days. In general, starting treatment earlier is better.
  - **Exclusion Criteria (at the time of remdesivir initiation).**
    - Consider excluding patients with COVID-19 who require invasive mechanical ventilation or ECMO. In the final remdesivir report, patients receiving mechanical ventilation or ECMO at enrollment did not see a statically significant improvement in recovery time (0.98, 95% CI 0.70 to 1.36).[6]
    - Consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.[5]
    - Incidental COVID positive cases without COVID symptoms found while screening.
- **Pregnant patients**
  - For pregnant patients, the same criteria for remdesivir therapy should be used as for non-pregnant patients.[11] Per the NIH guidelines, remdesivir should not be withheld from pregnant patients if it is otherwise indicated.[4] Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals.[12] In a study evaluating compassionate use of remdesivir in pregnant women with severe COVID-19, recovery rates were high and the rate of serious adverse events was low.[13]
- **Precautions, Adverse Reactions and Monitoring**
  - In all patients, before initiating remdesivir and during treatment as clinically appropriate, perform renal and hepatic laboratory testing and assess prothrombin time.[5]
  - Caution should be used when using remdesivir in patients with eGFR less than 30 mL/min. The package insert advises against use in these patients, however, risk versus benefit should be considered given lack of specific data on possible toxicity. Recent data suggests remdesivir may be safely used for short courses in patients with eGFR less than 30 mL/min or on hemodialysis.[14,15]

Remdesivir (Veklury)[5] (continued)

- **Precautions, Adverse Reactions and Monitoring (continued)**
  - Per the package label, hydroxychloroquine may result in reduced antiviral activity when coadministered with remdesivir. Hydroxychloroquine has a long half-life (~40 days). Waiting for hydroxychloroquine to eliminate from the body may result in missing the therapeutic window for remdesivir.[5]
  - 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 Patients**
  - Communicate to your patient or parent/caregiver information consistent with the Patient Information located at the end of the Veklury (remdesivir) package label: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf

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.[16]
- **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 using only high titer CCP and **only starting within the first 3 days of hospitalization** in patients who are older or with co-morbid conditions.[17] After this time, patients likely have their own COVID-19 antibodies.[18, 19] Given the results of the Mayo Clinic study (see below), CCP is not recommended for patients on mechanical ventilation.[18]
- In a recent meta analysis, treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all cause mortality or with any benefit for other clinical outcomes.[20] In addition, the NIH halted a trial of COVID-19 convalescent plasma in emergency department patients with mild symptoms due to lack of benefit.[21]
- The NIH's COVID-19 Treatment Guidelines Panel states that there are i**nsufficient 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.[2]
- There are **supply limitations** for obtaining CCP that **both limits the overall availability and potential timing of administration.**
- Evidence
  - In the Mayo Clinic study, there were 3082 adult patients at high-risk for progression to severe or life-threatening COVID-19 included. Death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients (27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti–SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32).[18]
  - In a study evaluating 464 adults (≥18 years) admitted to hospital with confirmed moderate covid-19, Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality.[19]
  - In a study evaluating 228 patients assigned to receive convalescent plasma and 105 to receive placebo, no significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days, and hypoxemia was the most frequent severity criterion for enrollment.[20]
- If available, CCP is supplied through the blood bank and not pharmacy.
- For patients who have received CCP, it is advised to wait at least 90 days to received a COVID-19 vaccine to avoid interference of the treatment with the vaccine-induced immune response.

Baricitinib in Combination with Remdesivir[21]

- The FDA issued an EUA for baricitinib (an oral Janus kinase (JAK) inhibitor), in combination with remdesivir, for suspected or laboratory confirmed COVID-19.
- **Patient population:** Hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
- **Evidence:**
  - In a clinical trial of hospitalized patients with COVID-19, the combination of baricitinib with remdesivir reduced time to recovery within 29 days after initiating treatment compared to patients who received a placebo with remdesivir.[24]
  - It is unknown how many patient received steroid therapy during the baricitinib studies.
  - The safety and effectiveness of this investigational therapy for use in the treatment of COVID -19 continues to be evaluated.
- There are insufficient data for the NIH Panel to r**ecommend either for or against the use** of baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized patients in cases where corticosteroids can be used instead.[2]
  - In the rare circumstances where corticosteroids cannot be used, the Panel recommends using baricitinib in combination with remdesivir for the treatment of COVID-19 in hospitalized, nonintubated patients who require oxygen

Baricitinib in Combination with Remdesivir[21] (continued)

supplementation (**BIIa**).[2, 9]
- The Panel **recommends against** the use of baricitinib in the absence of remdesivir, except in a clinical trial (**AIII**).[2]

- Baricitinib is available for COVID patients admitted to the hospital. Baricitinib is available from select specialty pharmacies for rheumatoid arthritis only.
- **Dose:**
  - Adults and pediatric patients 9 years of age and older: 4 mg orally once daily for 14 days or until hospital discharge (whichever comes first)
  - Pediatric patients 2 year to less than 9 years of age: 2 mg orally once daily for 14 days or until hospital discharge (whichever comes first)
- The **baricitinib patient fact sheet** (http://pi.lilly.com/eua/baricitinib-eua-factsheet-patient.pdf and http://pi.lilly.com/eua/span/baricitinib-eua-factsheet-patient-span.pdf) must be provided to patients and caregivers (available in English and Spanish).

Bamlanivimab[25]

- The FDA granted **emergency use authorization (EUA)** to bamlanivimab based on trial data showing that a one-time infusion of the treatment reduced the need for hospitalization or emergency room visits in high-risk COVID-19 patients. It was **not authorized for hospitalized patients** nor for those who require oxygen therapy due to COVID-19 as it could worsen clinical outcomes for such patients.
- **Patient eligibility[24]** Eligible patients have a COVID-19 positive test with symptom onset within 10 days
  - Mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.
    - High risk is defined as patients who meet at least one of the below criteria:
      - body mass index (BMI) ≥35
      - chronic kidney disease
      - diabetes
      - immunosuppressive disease
      - currently receiving immunosuppressive treatment
      - ≥65 years of age
      - Are ≥55 years of age AND have
        - cardiovascular disease, OR
        - hypertension,
        - chronic obstructive pulmonary disease
      - Are 12 – 17 years of age AND have
        - BMI ≥85th percentile for their age and gender based on CDC growth charts OR,
        - sickle cell disease, OR
        - congenital or acquired heart disease, OR
        - neurodevelopmental disorders, for example, cerebral palsy, OR
        - a medical-related technological dependence, (e.g., tracheostomy) OR
        - asthma other chronic respiratory disease that requires daily medication for control
- The **NIH has determined that bamlanivimab should not be considered the standard of care** for the treatment of patients with COVID-19. At this time, there are insufficient data to recommend either for or against the use of bamlanivimab for the treatment of outpatients with mild to moderate COVID-19.[2]
- The Infectious Diseases Society of America (IDSA) COVID-19 Guidelines[9]
  - For ambulatory patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited.
  - Among **hospitalized** patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)
- **Suggested use criteria** for adult patients (age 18 years or older)
  - The patient must have a positive COVID-19 test, be symptomatic with mild to moderate disease (within 10 days of symptom onset) and meet at least 1 to 2 high risk criteria listed below to qualify for bamlanivimab therapy. Therapy should be administered as soon as possible within 10 days of symptom onset.
    - Body mass index (BMI) ≥35
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease or currently receiving immunosuppressive treatment
    - ≥65 years of age
    - ≥55 years of age AND have one of the following
      - cardiovascular disease OR
      - hypertension OR
      - chronic obstructive pulmonary disease or other uncontrolled chronic respiratory disease
  - Exclusion criteria
    - Patients hospitalized for COVID-19[25]
    - Patients who require new oxygen therapy or an increase in oxygen therapy due to COVID-19 (it could worsen clinical outcomes for such patients)
- **For children (age 12 to 17)**, use patient eligibility criteria in the bamlanivimab EUA (see above)
- **Availability.** Order directly from AmerisourceBergen Corporation (ABC); the product is no longer under allocation.
- **Dose and Setting:** Bamlanivimab should be administered as a single 700 mg IV infusion post-dilution (0.9% Sodium Chloride) via an infusion pump or gravity. The infusion is intended for administration in an outpatient setting with at least an additional hour of observation upon completion for anaphylaxis or infusion-related reactions. It is recommended to have anaphylaxis kits readily available.
- A new warning was added to EUA: **Clinical Worsening After Bamlanivimab Administration**: Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia

Bamlanivimab[23] (continued)

or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.[26]

- For patients who have received bamlamivimab, it is advised to wait at least 90 days to received a COVID-19 vaccine to avoid interference of the treatment with the vaccine-induced immune response.
- There is no data to support preference for bamlanivimab or the combination of casirivimab and imdevimab at this time for the identified patient population.
- Bamlanivimab is not considered a hazardous drug.
- The **bamlanivimab patient fact sheet** (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-patient.pdf) must be provided to patients and caregivers.
- The **bamlanivimab provider fact sheet** contains additional pertinent information (http://pi.lilly.com/eua/bamlanivimab-eua-factsheet-hcp.pdf)

Casirivimab and Imdevimab [27]

- The FDA issued an EUA for casirivimab and imdevimab to be administered together for the treatment of mild to moderate COVID-19.
  - **Patient population:**
    - Adults and pediatric patients (12 years of age or older weighing at least 40 kilograms) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progressing to severe COVID-19.
    - High risk is defined as patients who meet at least one of the below criteria:
      - body mass index (BMI) ≥35
      - chronic kidney disease
      - diabetes
      - immunosuppressive disease
      - currently receiving immunosuppressive treatment
      - ≥65 years of age
      - Are ≥55 years of age AND have
        - cardiovascular disease, OR
        - hypertension,
        - chronic obstructive pulmonary disease
      - Are 12 – 17 years of age AND have
        - BMI ≥85th percentile for their age and gender based on CDC growth charts OR,
        - sickle cell disease, OR
        - congenital or acquired heart disease, OR
        - neurodevelopmental disorders, for example, cerebral palsy, OR
        - a medical-related technological dependence, (e.g., tracheostomy) OR
        - asthma other chronic respiratory disease that requires daily medication for control
- Casirivimab and imdevimab are **not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19**. Treatment with these monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
- **Evidence:**
  - In a clinical trial of patients with COVID-19, casirivimab and imdevimab, administered together via IV infusion, were shown to reduce COVID-19-related hospitalization or emergency room visits in patients at high risk for disease progression within 28 days after treatment when compared to placebo.
  - The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated.
- **Suggested use criteria** for adult patients (age 18 years or older)
  - The patient must have a positive COVID-19 test, be symptomatic with mild to moderate disease (within 10 days of symptom onset) and meet at least 1 to 2 high risk criteria listed below to qualify for bamlanivimab therapy. Therapy should be administered as soon as possible within 10 days of symptom onset.
    - Body mass index (BMI) ≥35
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease or currently receiving immunosuppressive treatment
    - ≥65 years of age
    - ≥55 years of age AND have
      - cardiovascular disease, OR
      - hypertension, OR
      - chronic obstructive pulmonary disease/other uncontrolled chronic respiratory disease
    - Exclusion criteria
      - Patients hospitalized for COVID-19[28]
      - Patients who require new oxygen therapy or an increase in oxygen therapy due to COVID-19 (it could worsen clinical outcomes for such patients)
- **For children (age 12 to 17)**, use patient eligibility criteria in the bamlanivimab EU (see above)
- **Availability.** Order directly from AmerisourceBergen Corporation (ABC); the product is no longer under allocation.
- A new warning was added to EUA: **Clinical Worsening After Casirivimab with imdevimab Administration:** Clinical worsening of COVID-19 after administration of casirivimab with imdevimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.[29]
- **Dose:** 1200 mg of casirivimab and 1200 mg of imdevimab administered as a single intravenous infusion over at least 60 minutes as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset. Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete. It is recommended to have anaphylaxis kits readily available.

Casirivimab and Imdevimab [27] (continued)

- At this time, the NIH has determined there are **insufficient data to recommend either for or against** the use of casirivimab plus imdevimab for the treatment of outpatients with mild to moderate COVID-19. The casirivimab plus imdevimab combination should not be considered the standard of care for the treatment of patients with COVID-19.[2]
- The Infectious Diseases Society of America (IDSA) COVID-19 Guidelines[9]
  - For ambulatory patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited.[9]
- The **casirivimab and imdevimab patient fact sheet** (https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-patient.pdf and https://www.regeneron.com/sites/default/files/treatment-covid19-eua-fact-sheet-for-patient-spanish.pdf) must be provided to patients and caregivers (available in English and Spanish).
- Casirivimab and imdevimab are not considered a hazardous drugs.
- For patients who have received casirivimab and imdevimab, it is advised to wait at least 90 days to received a COVID-19 vaccine to avoid interference of the treatment with the vaccine-induced immune response.
- There is no data to support preference for bamlanivimab or the combination of casirivimab and imdevimab at this time for the identified patient population.

Bamlanivimab & Etesevimab[30]

- The FDA granted **emergency use authorization (EUA)** to the combination of bamlanivimab & etesevimab to be administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.
- As of the date of this guideline, bamlanivimab & etesevimab is not yet available at CommonSpirit Health.
- Bamlanivimab and etesevimab are not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in
  - those on chronic oxygen therapy due to underlying non COVID-19 related comorbidity.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.
- High risk is defined as patients who meet at least one of the below criteria:
  - body mass index (BMI) ≥35
  - chronic kidney disease
  - diabetes
  - immunosuppressive disease
  - currently receiving immunosuppressive treatment
  - ≥65 years of age
  - Are ≥55 years of age AND have
    - cardiovascular disease, OR
    - hypertension,
    - chronic obstructive pulmonary disease
  - Are 12 – 17 years of age AND have
    - BMI ≥85th percentile for their age and gender based on CDC growth charts OR,
    - sickle cell disease, OR
    - congenital or acquired heart disease, OR
    - neurodevelopmental disorders, for example, cerebral palsy, OR
    - a medical-related technological dependence, (e.g., tracheostomy) OR
    - asthma other chronic respiratory disease that requires daily medication for control
- **Suggested use criteria** for adult patients (age 18 years or older) to allow judicious use of medication while it is on federal allocation
  - The patient must have a positive COVID-19 test, be symptomatic with mild to moderate disease (within 10 days of symptom onset) and meet at least 1 to 2 high risk criteria listed below to qualify for bamlanivimab therapy. Therapy should be administered as soon as possible within 10 days of symptom onset.
    - Body mass index (BMI) ≥35
    - Chronic kidney disease
    - Diabetes
    - Immunosuppressive disease or currently receiving immunosuppressive treatment
    - ≥65 years of age
    - ≥55 years of age AND have
      - cardiovascular disease, OR
      - hypertension, OR
      - chronic obstructive pulmonary disease/other uncontrolled chronic respiratory disease
  - Exclusion criteria
    - who are hospitalized due to COVID-19, OR
    - who require oxygen therapy due to COVID-19, OR
    - who require an increase in baseline oxygen flow rate due to COVID-19 in
    - those on chronic oxygen therapy due to underlying non COVID-19 related comorbidity.
- **Dose:** 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within ten days of symptom onset.
- NIH Recommendations[2]
  - The Panel **recommends** the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria (BIIa). Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset.

Bamlanivimab & Etesevimab[30] (continued)

- The Panel r**ecommends against** the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for patients who are hospitalized because of COVID-19, except in a clinical trial. However, the combination should be considered for persons with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19 but who otherwise meet the EUA criteria.

- The Infectious Diseases Society of America (IDSA) COVID 19 Guidelines[9]
  - Among **ambulatory patients** with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab rather than no bamlanivimab/etesevimab. (Conditional recommendation, low certainty of evidence)
    - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab.
    - For patients at high risk for progression to severe disease, the data are strongest for bamlanivimab/etesevimab. Bamlanivimab monotherapy or casirivimab/imdevimab may have similar clinical benefit, but data are more limited.
    - There are limited data on efficacy of bamlanivimab/etesevimab in high risk patients between 12 and 18 years of age.
- The **bamlanivimab & etesevimab patient fact sheet** (http://pi.lilly.com/eua/bam-and-ete-eua-factsheet-patient.pdf and http://pi.lilly.com/eua/span/bam-and-ete-eua-factsheet-patient-span.pdf) must be provided to patients and caregivers (available in English and Spanish)
- For patients who have received b amlanivimab & etesevimab, it is advised to wait at least 90 days to received a COVID-19 vaccine to avoid interference of the treatment with the vaccine induced immune response.

Recommended language for EUA medication initiation

- I spoke with _(patient/healthcare proxy)_ to provide information about [EUA medication] for _(patient)_
- I offered them the "Fact Sheet for Patients and Parents/Caregivers" for [EUA medication] 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 [risks/adverse reactions]
- 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 [EUA medication] treatment, but the therapy has not been fully evaluated in pregnant patients
- Offered opportunity to ask questions and all questions were answered
- _(patient/healthcare proxy)_voiced understanding and agreed to proceed with treatment for _(patient)_

Risks/adverse reactions for current [EUA medications] include:

- **COVID convalescent plasma:** 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.
- **Baricitinib in Combination with Remdesivir:** serious venous thrombosis, including pulmonary embolism, serious infections, hypersensitivity.
- **Bamlanivimab, Casirivimab & Imdevimab, and Bamlanivimab & Etesevima:** anaphylaxis, clinical worsening of COVID-19 and infusion related reactions. Infusion-related reactions may include fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

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- **Anticoagulation** (supplemental to information on page 1). 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.[31]
  - 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 x10^9/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.[4]
- **Steroids** (supplemental to information on page 1). Recommendations are based on the results of the RECOVERY trial[32]
  - Patients with severe ARDS may require higher steroid doses.[33]
  - Oral dexamethasone is preferred over IV if a patient can take oral medications.
  - 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.[9]
  - 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*.[34]
- **IL-6 inhibitors** (e.g., tocilizumab (Actemra)).
  - Per the NIH guidelines[2]
    - The Panel recommends the use of tocilizumab (single intravenous dose of 8 mg/kg of actual body weight, up to 800 mg) in combination with dexamethasone (6 mg daily for up to 10 days) in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19. These patients are:
      - Recently hospitalized (within 3 days) patients who have been admitted to an intensive care unit (ICU) within the

Medication Considerations (continued)

prior 24 hours and who require invasive mechanical ventilation, noninvasive mechanical ventilation (NIV) or high-flow nasal canula (HFNC) oxygen (>0.4 FiO2/30 L/min of oxygen flow) (BIIa); or
- Recently hospitalized patients (not in an ICU) with rapidly increasing oxygen needs who require NIV or HFNC and have signific antly increased markers of inflammation (BIIa). (Note: The RECOVERY trial inclusion criterion for inflammation was C-reactive protein [CRP] ≥75 mg/L).
- There is insufficient evidence to specify which hospitalized patients with hypoxemia who require conventional oxygen therapy would benefit from the addition of tocilizumab.

- Per the IDSA guidelines[9]
  - Among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)
    - *Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental
    - **Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.
    - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.
    - In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L.
  - **Restriction Criteria (based on currently available information):** Facilities may use more restrictive criteria.
    - **Use Criteria (must meet all)**
      - Suggest for patients who are within 24 hours of decompensation to requiring invasive or noninvasive mechanical ventilation or high-flow oxygen (>0.4 FiO2/30 L/min oxygen flow) and have elevated CRP ≥75 mg/L (≥7.5 mg/dL) and are also exhibiting rapid progression of respiratory failure (note low certainty of evidence)
      - Single dose of tocilizumab (8 mg/kg of actual body weight, up to 800 mg) only
      - Must use in addition to dexamethasone or other steroids
      - Restrict tocilizumab initiation to infectious disease providers (if available in a timely manner)
    - **Exclusion criteria.** Use of tocilizumab should be avoided in patients with any of the following:
      - Significant immunosuppression, particularly in those with a history of recent use of other biologic immunomodulating drugs
      - Alanine transaminase >5 times the upper limit of normal
      - High risk for gastrointestinal perforation
      - Uncontrolled, serious bacterial, fungal, or non-SARS-CoV-2 viral infection (e.g., active tuberculosis)
      - Absolute neutrophil count <500 cells/μL
  - In the RECOVERY trial that evaluated tocilizumab, benefit was seen in hospitalized COVID patients with hypoxia and systemic inflammation (especially in those receiving systemic steroids).[35]
  - The studies reviewing IL 6 inhibitors for treating COVID 19 are mixed.[35–39]
- **Hyperglycemia management.** Monitor blood glucose for all COVID or PUI patients. Treat hyperglycemia proactively. Well controlled blood glucose has been associated with better outcomes in COVID patients.[40, 41]
- **Influenza vaccination.** Although data are lacking on influenza vaccination for persons with COVID-19, on the basis of practice for other acute respiratory infections, the NIH Panel recommends that persons with COVID-19 should receive an inactivated influenza vaccine (BIII).[4]
- The overview of **IDSA COVID-19 Treatment Guidelines** (updated 12/2/2020) can be found here: https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/overview-of-covid-19-interventions-v3.5.1.pdf
- 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.
- **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.[42]
  - 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.
- **ACE Inhibitors**. Persons with COVID-19 who are prescribed ACE inhibitors or ARBs for cardiovascular disease (or other indications) should continue these medications (AIII). The COVID-19 Treatment Guidelines Panel (the Panel) recommends against the use of ACE inhibitors or ARBs for the treatment of COVID-19, except in a clinical trial (AIII).[2]
- **Statins.** Persons with COVID-19 who are prescribed statin therapy for the treatment or prevention of cardiovascular disease should continue these medications (AIII). The Panel recommends against the use of statins for the treatment of COVID -19, except in a clinical trial (AIII).[2]
- **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

Medication Considerations (continued)

tapered off. This is a weak recommendation, with very low quality evidence.[43]

- **FDA website available on COVID-19:** https://www.fda.gov/health-professionals/coronavirus-disease-2019-covid-19-resources-health-professionals

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.** The NIH panel recommends against chloroquine or hydroxychloroquine for the treatment of COVID-19, except in a clinical trial (AII).[2] The FDA has withdrawn the EUA for hydroxychloroquine and chloroquine.[44] The NIH and WHO have terminated their randomized, controlled studies assessing hydroxychloroquine due to lack of efficacy.[45] Trials have shown no benefit of hydroxychloroquine for patients with COVID-19.[46-48]
- **Hydroxychloroquine and azithromycin.** Do not use for COVID-19.[2]
- **Prophylaxis with hydroxychloroquine.** Prophylaxis should not be utilized based on results from a large, US based, randomized, placebo controlled trial.[49]
- **Ivermectin.** The FDA has stated to not use ivermectin to treat or prevent COVID-19.[50] The NIH has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19. Most of the studies reported to date evaluating ivermectin had incomplete information and significant methodological limitations, which make it difficult to exclude common causes of bias.[2] There is currently a nation-wide shortage of ivermectin.
- **Kaletra (lopinavir-ritonavir).** In a recent in vivo study, it did not show benefit compared to standard of care.[51] The NIH recommends against the use of this therapy at this time.[2] Additional studies are ongoing, including those with combination therapy.
- **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.[52]
- **Ribavirin.** There is no evidence to support ribavirin monotherapy as a treatment for COVID-19 at this time.
- **Alteplase.** For a known PE or stroke, use continues to be recommended.
- **Ascorbic acid.** Do not use IV ascorbic acid.
- IL-1 inhibitors (e.g., anakinra) (insufficient data)[2,53]
- Melatonin
- Pioglitazone
- Zinc
- Thiamine
- IVIG. Do not use.
- Interferons. Do not use.
- Famotidine[54]
- Acetazolamide
- Acalabrutinib[55]
- Quercetin
- Colchicine[56]
- Oseltamivir
- Vitamin D
- Fenofibrate
- Fluvoxamine

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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