UCHealth COVID-19 Pharmacotherapy Guidance

Outpatient Prevention:

PATIENT DISPOSITION	•RECOMMENDATION
Outpatient, post-exposure prophylaxis	•**COVID-19 monoclonal antibodies (mAb)** are recommended for high-risk, patients who are not fully vaccinated or who are not expected to mount an adequate immune response to complete vaccination and have been exposed to an individual infected with SARS-CoV-2, or who are at high risk of exposure because of occurence of infection in the same institutional setting.

Outpatient Treatment:

PATIENT DISPOSITION	•RECOMMENDATION
Outpatient, not requiring hospitalization or supplemental oxygen	•**COVID-19 monoclonal antibodies (mAb)** are recommended for high-risk, symptomatic patients within 10 days of symptom onset.
Discharged from hospital, not requiring supplemental oxygen	•No specific antiviral or immunomodulatory therapy recommended.
Discharged from hospital, requiring supplemental oxygen ***(for those stable enough for discharge but still requiring oxygen)***	•Consider continuing **dexamethasone** for the duration of supplemental oxygen requirement, up to 10 days total dexamethasone duration, with close monitoring for adverse events.
Discharged from ED or urgent care, despite new oxygen requirement *(when hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured)*	•**Dexamethasone** 6 mg PO daily for the duration of supplemental oxygen need, up to 10 days maximum, with close monitoring for adverse events.

Inpatient Treatment:

DISEASE SEVERITY	•RECOMMENDATION
Hospitalized, not requiring supplemental oxygen	•No specific antiviral or immunomodulatory therapy recommended. •Consider passive antibody treatment with mAb (if meets EUA criteria) or convalescent plasma in patients who are known or suspected to have poor intrinsic humoral immunity.
Hospitalized, requiring low-flow supplemental oxygen	•Use: **Remdesivir** *plus* **Dexamethasone**
Hospitalized, requiring oxygen via high-flow device or noninvasive ventilation	•Use: **Dexamethasone** •Consider: **Remdesivir** in patients who are early in their disease course (<10 days of symptom onset); otherwise low likelihood of benefit at this disease severity. •Consider: **Baricitinib**, in combo with dexamethasone, for recently hospitalized patients with rapidly increasing oxygen needs and systemic inflammation. Tocilizumab may be considered if baricitinib is contraindicated. Consider assessing reponse to steroids before deciding whether baricitinib is needed.
Hospitalized, requiring invasive mechanical ventilation or ECMO	•*For most patients*, use: **Dexamethasone** •*For patients who are within 24hrs of ICU admission and mechanical ventilation*, consider: **Tocilizumab**, in combination with dexamethasone.

Adapted from NIH COVID-19 Treatment Guideline

COVID-19 Therapies at UCHealth: Indications, Drug Information, Ordering Information

SARS-CoV-2 Monoclonal Antibodies

COVID-19 monoclonal antibodies (mAbs) are laboratory-derived neutralizing antibodies against the SARS-CoV-2 spike protein. mAbs are used primarily for outpatient treatment or post-exposure prophylaxis, with potential for inpatient use in select cases. Given early, mAbs can shorten duration of symptoms and prevent hospitalization and death. mAbs are available under Emergency Use Authorization (EUA) for COVID-19 treatment and post-exposure prophylaxis.

Available mAbs:

1. **Casirivimab/Imdevimab** (REG-COV-2; Regeneron). Preferred agent at UCHealth. Retains activity against currently circulating variants including alpha, beta, gamma, and delta.
2. Sotrovimab (GSK): Active against currently circulating variants; not available at UCHealth presently.
3. Bamlanivimab/etesevimab combination: re-authorized 8/23/21 in states where resistant variants <5% of circulating virus (including Colorado); not currently available at UCHealth.

Note: Bamlanivimab monotherapy no longer recommended (EUA revoked), due to loss of activity against some SARS-CoV-2 variants.

Treatment Criteria (for age ≥12 years, weight ≥40kg):

1. Confirmed COVID-19 (by PCR or antigen test)
2. Mild-moderate (symptomatic) disease, not requiring supplemental O2
3. Symptom duration ≤ 10 days
4. High risk for progression to severe disease (see EUA high-risk criteria below)

Treatment Exclusions:

- Hospitalization due to COVID-19
- New oxygen requirement or increase in oxygen flow rate from baseline (SpO2 < 90%)

Notes:

- Select **inpatients** may be considered for mAbs who meet the above criteria and:
    - Are hospitalized for another reason (i.e., are not hospitalized due to COVID-19)
    - Are known to be seronegative or postulated to have impaired humoral immune response
    - *At AMC please send inpatient requests via secure chat to "AMC Antimicrobial Stewardship" group.*
- Patients who receive passive antibody therapy (mAbs or convalescent plasma) are recommended to defer COVID-19 vaccination for 90 days, to avoid potential interference with vaccine-induced immune response.

Post-Exposure Prophylaxis (PEP) Criteria* (for age ≥12 years, weight ≥40kg):

EITHER:

1. High risk for progression to severe disease (see EUA high-risk criteria below), OR
2. Not fully vaccinated or not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (e.g., individuals with immunocompromising conditions including immunocompromising medications)

AND one of the following:

a. Exposure to an individual infected with SARS-CoV-2 (within 6 feet for a total of 15 minutes or more, providing care to someone who is sick, direct physical contact, sharing utensils, or exposure to respiratory droplets), OR
b. High risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of infection in other individuals in the same institutional setting (e.g. nursing homes, prisons).

*UCHealth is aware of the indication for PEP, and its priority currently is to offer mAb therapy to patients with known COVID-19 infections. Options for expanding access are being investigated.

FDA mAb EUA Criteria for high-risk of progression to severe disease (updated 5/14/21):

- Older age (age ≥ 65 years)
- Obesity or overweight (BMI ≥ 25 kg/m^2, or BMI ≥85th percentile if age 12-17 years)
- Pregnancy
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppressive disease or treatment, including HIV infection
- Cardiovascular disease (including congenital heart disease and cerebrovascular disease) or hypertension
- Chronic lung disease (e.g., COPD, asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension, or current/former smoker)
- Sickle cell disease
- Neurodevelopmental disorders including cerebral palsy or genetic, metabolic syndromes or severe congenital abnormalities
- Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation)
- Other medical conditions or factors placing an individual patient at high risk for progression to severe disease (e.g., race or ethnicity, people with disabilities, substance use disorder, others)

NIH statement on mAb prioritization in the event of shortage or logistical constraints (*NEW 9/3/21*): NIH COVID-19 Treatment Guidelines Panel suggests that in situations where it is necessary to triage eligible patients, priority should go to:

- COVID-19 treatment over PEP
- Treatment of unvaccinated/incompletely vaccinated individuals at high-risk of progression to severe disease and vaccinated individuals who are not expected to mount an adequate immune response (e.g. immunocompromised) over vaccinated individuals who are expected to have mounted an adequate immune response

Ordering: see information on the Source for outpatient UCHealth infusion sites, patient prioritization, and ordering instructions.

Remdesivir (Veklury; RDV):

Remdesivir is FDA-approved for the treatment of COVID-19 requiring hospitalization in adults and pediatrics (≥ 12 years and weighing ≥ 40 kg).

Criteria for use:

1. Confirmed COVID-19 by SARS-CoV-2 PCR
2. Symptom duration ≤14 days (longer duration considered if transplant recipient or other severely immunocompromised host)
3. Hypoxia requiring supplemental O_2
   - Patients requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and/or ECMO at baseline are unlikely to benefit from RDV based on current evidence.
   - May continued RDV if patients progress to mechanical ventilation or ECMO.
4. ALT <10x ULN

Dose: 200 mg on day 1, then 100 mg on days 2-5

Duration: 5 days or until hospital discharge (whichever is sooner)

Ordering and monitoring:

- Monitor LFTs daily. Consider discontinuation if ALT >10x ULN.
- Renal impairment (including CrCl < 30 mL/min and renal replacement therapy (e.g. CRRT, iHD, PD)) is not a contraindication to RDV. The RDV package insert recommends against use among patients with CrCl < 30

mL/min due to the potential for cyclodextrin and RDV accumulation leading to worsening renal failure. However, given the small amount of cyclodextrin in RDV and short duration of exposure, adverse events are unlikely, and no increased risk of serious or non-serious safety events (including renal or hepatotoxicity) have been observed in several retrospective studies.

Approval:

- At UCHealth AMC, RDV is a tier-2 protected antimicrobial (i.e., order is approved by verifying pharmacist if criteria above are met).
- Requests not meeting the above criteria can be made via the Antimicrobial Stewardship secure chat group to "AMC Antimicrobial Stewardship."

Dexamethasone

Dexamethasone is indicated in patients requiring supplemental O_2 for COVID-19, including mechanical ventilation or ECMO. It is NOT recommended in those not requiring supplemental O2.

Dose: 6 mg IV or PO per day

Duration: 10 days, or until hospital discharge. If patient requires a brief hospitalization and still requiring increased oxygen support, consider discharging to complete a 5-7 days course. Alternative glucocorticoids can be considered if dexamethasone is unavailable:

- Prednisone 40 mg per day
- Methylprednisolone 32 mg per day (once daily or 2 divided doses)
- Hydrocortisone 160 mg per day (2-4 divided doses)

Note: Recommend consultation with Maternal Fetal Medicine regarding the use of steroids in pregnant patients

Tocilizumab (Actemra)

Tocilizumab is an IL-6 receptor antagonist used for treatment of rheumatoid arthritis and cytokine-release syndrome associated with CAR-T cell therapy. It had prior mixed results for COVID-19 treatment, but two recent trials (REMAP-CAP, RECOVERY) suggest a mortality benefit when used **with corticosteroids** in a select population of hospitalized patients who are exhibiting rapid respiratory decompensation. Consider as an adjunct therapy to steroids for patients who are recently admitted (hospitalization <3 days) and are:

- Newly admitted to the ICU (within 24hr) with high O2 need (HFNC FiO2 >0.4/flow rate 30L/min, NIV, MV)
- Not yet admitted to ICU but with rapidly increasing O2 need requiring HFNC or NIV, AND have significantly elevated inflammatory markers (CRP >= 75 mg/L)

Other considerations:

- Consider assessing response to corticosteroids (e.g. 48 hrs) prior to deciding whether tocilizumab is needed
- Tocilizumab has not been shown to have benefit in patients already requiring mechanical ventilation (unless newly intubated <24 hrs)
- Tocilizumab should be AVOIDED in:
    - Severely immunocompromised hosts
    - Suspected or confirmed other concurrent infection
    - AST/ALT >5x ULN
    - ANC <500, platelets <50K
    - High risk for GI perforation
    - Pregnancy: risk vs. benefit, recommend consultation with Maternal Fetal Medicine
- Monitor for development of new, or re-activation of latent, infections
- Consider screening for latent infections depending on risk factors (e.g. TB, strongyloides, others)
- Consider prophylactic treatment with ivermectin in patients from strongyloides-endemic areas
- Monitor following tocilizumab administration: neutrophils, platelets, LFTs

Dosing: 8mg/kg x 1 dose, rounded as below. Unclear benefit of additional doses.

- 40 kg to 65 kg = 400mg using IV formulation→324mg if using the SQ syringe for compounding
- 66 kg to 90 kg = 600mg using IV formulation→648mg if using the SQ syringe for compounding
- > 90kg = 800mg using IV formulation→810mg if using the SQ syringe for compounding

Baricitinib (Olumiant)

Baricitinib is an oral Janus kinase (JAK) inhibitor that is used for rheumatoid arthritis treatment (non-formulary at UCH). Some data has shown improved time to recovery when given with RDV in patients requiring supplemental O2 (ACTT-2, Dec 2020), and lower 28-day all-cause mortality when given with either dexamethasone or dexamethasone + RDV) in patients requiring supplemental oxygen or high-flow/NIV (excluded baseline mechanical ventilation). The benefit of baricitinib in this trial was most pronounced among those requiring HFNC/NIV at baseline. (COV-BARRIER, May 2021 pre-print).

Based on this, NIH Guideline recommends that for hospitalized patients on high-flow oxygen or NIV who have evidence of clinical progression or increased markers of inflammation, may use either:

- Baricitinib OR tocilizumab plus dexamethasone alone, or
- Baricitinib OR tocilizumab plus dexamethasone + remdesivir
- In the rare circumstance when corticosteroids cannot be used, may use baricitinib + RDV for hospitalized, non-intubated pts requiring supplemental O2

Indication:
At UCH, baricitinib will be the preferred add-on treatment to dexamethasone for patients with COVID-19 who are:

- Hospitalized < 72 hours
- Experience worsening respiratory function despite dexamethasone who require HFNC or NIV
- Persistently elevated/increasing C-reactive protein

Dosing:

- 4mg once daily x 14 days (may discontinue use sooner than 14 days if patient otherwise recovered and discharging from hospital – do not continue after hospital discharge)
- eGFR:
    - ≥ 60 mL/min/1.73m^2 = 4mg once daily
    - 30-59 mL/min/1.73m^2 = 2mg once daily
    - 15-29 mL/min/1.73m^2 = 1mg daily or 2mg q48h
    - < 15 mL/min/1.73m^2 = hold and resume dosing once eGFR > 15 mL/min/1.73m^2
- ALC < 200: hold dose, can resume once ALC > 200
- ANC < 500: hold dose, can resume once ANC > 500
- Increase in AST or ALT to >5-10x ULN concerning for DILI: hold dose until diagnosis of DILI is excluded

Other considerations:

- Consider assessing response to corticosteroids (e.g. 48 hrs) prior to deciding whether baricitinib is needed
- Baricitinib has not been evaluated among patients requiring mechanical ventilation at baseline, but may be continued among patients initiated on baricitinib in whom subsequently progress to mechanical ventilation who.
- Baricitinib should be AVOIDED in:
    - eGFR (non-race based result) < 15 mL/min/1.73m^2
    - Any for of renal replacement therapy
    - Known active tuberculosis (routine quantiferon screening not required if no epidemiologic risk factors)
    - Absolute lymphocyte count (ALC) < 200 cells/µL (aka 0.2 x 10^9/L) – may be started/resumed once ALC improves to > 200

  - Absolute neutrophil count (ANC) < 500 cells/µL (aka 0.5 x 10^9/L) – may be started/resumed once ANC improves to > 500
  - Hemoglobin < 8g/dL
  - Pregnancy: risk vs. benefit, recommend consultation with Maternal Fetal Medicine
- Screen for drug-drug interactions
- Monitor CBC and BMP daily, LFTs weekly, and for development of new, or re-activation of latent, infections

Convalescent Plasma

COVID-19 convalescent plasma (CCP) is plasma obtained from donors who have previously recovered from COVID-19, and contains neutralizing antibodies to SARS-CoV-2. CCP has previously received emergency use authorization (EUA) for COVID-19 treatment; however, studies have shown mixed results and recent studies show no clinical benefits in hospitalized patients, including with high-titer plasma.

- Convalescent plasma is not recommended for routine use in hospitalized or non-hospitalized patients; rather, it is recommended to be used in the context of a clinical trial.
- EUA convalescent plasma is available through the blood blank (all units have high-titer neutralizing antibody) if use is desired outside of a clinical trial (e.g., if patient is felt to benefit from passive immunity but is not eligible for mAb therapy).