## Overview of COVID-19 Treatment Recommendations

### Outpatient, not requiring supplemental oxygen
- Consider SARS-COV-2 monoclonal antibodies among high risk, symptomatic patients. See page 3 for details.

### Hospitalized, not requiring supplemental oxygen
- No specific antiviral or immunomodulatory therapy recommended.

### Hospitalized or not hospitalized, requiring low-flow supplemental oxygen

**Hospitalized and requiring supplemental oxygen:**
- **Remdesivir plus Dexamethasone**
  - Remdesivir: 200 mg IV x 1, then 100 mg daily x 4 days (5 day max duration); continue if patient progresses to high-flow, NIV, or mechanical ventilation.
  - Dexamethasone: 6 mg IV or PO daily for up to 10 days or until hospital discharge, whichever comes sooner. If brief hospitalization, consider discharging to complete 5-7 days dexamethasone if requiring home oxygen.

**Not Hospitalized, but requiring oxygen for COVID-19**
- Consider Dexamethasone 6 mg PO daily x 5-7 days.

### Hospitalized, requiring oxygen via high-flow device or noninvasive ventilation
- Dexamethasone. Dose as above. Remdesivir not recommended at this stage of disease.
- Tocilizumab may be considered for patients who experience clinical worsening on dexamethasone after 48 hours AND are receiving high-flow NC > 30 L/min and FiO2 > 0.4 with CRP ≥ 75 mg/L. See following pages for dosing.

### Hospitalized, requiring invasive mechanical ventilation or ECMO
- Dexamethasone. Dose as above. Remdesivir not recommended at this stage of disease.
- Tocilizumab may be considered as an adjunct to dexamethasone for patients within 24 hours of mechanical ventilation without improvement in respiratory function and worsening inflammatory markers.
**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).

**I. 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 O₂
   - 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.
     - Remdesivir may be continued if patients progress to mechanical ventilation or ECMO.
4. ALT <10x ULN

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

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

**IV. Ordering and monitoring:**
- Monitor LFTs daily. Consider discontinuation if ALT >10x ULN.
- Renal impairment is not a contraindication to RDV.
- Patients with CrCl < 30 mL/min and those receiving renal replacement therapies (e.g. CRRT, iHD, PD) can be considered for 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. Despite higher metabolite and cyclodextrin exposure, no increases risk serious or non-serious safety events have been observed; several retrospective studies have not identified increased rates of renal or hepatic adverse events in patients with severe renal impairment or on renal replacement therapy.

**V. Approval**
- At UCHealth AMC, RDV is a tier 2 protected antimicrobial (i.e., order is approved by verifying pharmacist if criteria above are met).
- Requested outside of criteria can be made via the Antimicrobial Stewardship secure chat group to “AMC Antimicrobial Stewardship.”

**Dexamethasone**

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

**I. Dose:** 6 mg IV or PO per day

**II. 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.

**III. 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)

**IV. Note:** Recommend consultation with OB/GYN regarding the use of steroids in pregnant patients.
Anti-SARS-CoV-2 Monoclonal Antibodies:
Bamlanivimab, Casirivimab + Imdevimab, Bamlanivimab + Etesevimab

Anti-SARS-CoV-2 monoclonal antibodies (mAbs) are laboratory-derived neutralizing antibodies against the SARS-CoV-2 spike protein. Criteria for mAb use at UCHealth follows CDPHE guidance adhering to FDA EUA criteria, and requires submission to a random allocation system prior to placing an order, to determine if patient will be able to receive one of these products. See attached pages for additional information.

I. Criteria for use:
1. Ambulatory patients not requiring hospitalization for COVID-19
2. Confirmed COVID-19 by SARS-CoV-2 PCR or Antigen
3. Duration of symptoms ≤ 10 days
4. Not requiring new O₂ therapy or an increase in baseline O₂ flow rate due to COVID-19 (SpO₂ <90%)
5. Has ≥ 1 of the following risk factors for high risk of progression to severe disease:
   - BMI ≥ 35 kg/m²
   - Chronic kidney disease
   - Diabetes mellitus
   - Immunocompromised state
   - Age ≥ 65 years
   - Age ≥ 55 years AND have cardiovascular disease, hypertension, or COPD/other chronic respiratory disease
   - Age 12-17 years AND have BMI ≥ 85th percentile, sickle cell disease, congenital or acquired heart disease, neurodevelopmental disorders, medical-related technological dependence (e.g. tracheostomy), or asthma, reactive airway disease, or other chronic respiratory disease that requires daily medication for control

II. Currently Available EUA mAbs:
1. Casirivimab + Imdevimab (REG-COV-2; Regeneron, mAb combination). This is currently the preferred agent due to stability of in vitro activity against South African (B.1.351), recently detected in Colorado, where other monoclonals have 10-fold reduced activity.
2. Bamlanivimab + Etesevimab (Eli Lilly, mAb combination)
3. Bamlanivimab (Eli Lilly, single mAb)

III. Inpatient Ordering: mAbs may be considered for patients who meet the above criteria but are hospitalized for another reason (i.e., are not hospitalized due to COVID-19); at AMC please send inpatient requests via secure chat to “AMC Stewardship” group.

Notes:
- mAb combinations (CAS+IMD, BAM+ETE) are preferred over single mAb product (BAM) for likely improved effectiveness and decreased potential for mutational escape.
- mAbs are not FDA-approved products and not considered standard of care; clinical judgment and shared, informed decision-making should be exercised when considering use for individual patients.
- 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.

Baricitinib (Olumiant)

Baricitinib is an oral Janus kinase (JAK) inhibitor, which has been granted EUA for use in combination with RDV in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental O₂, invasive mechanical ventilation, or ECMO.

I. In ACTT-2 the median time to recovery (TTR) was shorter in the baricitinib plus RDV group (7 days) than in the placebo plus RDV group (8 days) (rate ratio 1.16; 95% CI, 1.01–1.32; P = 0.03). However, there was no statistically significant difference in Day-28 mortality (OR 0.65; 95% CI, 0.39–1.09).

II. Given lack of mortality benefit among overall cohort and subgroups requiring high-flow/NIV and mechanical ventilation, baricitinib is not expected to provide benefit over dexamethasone and is NOT recommended.
Tocilizumab

Tocilizumab is an IL-6 receptor antagonist that may be considered as an adjunct therapy for patients who experience clinical worsening on dexamethasone after 48 hours AND are receiving high-flow NC > 30 L/min and FiO2 > 0.4 with CRP ≥ 75 mg/L. Two trials (REMAP-CAP, RECOVERY) have suggested that tocilizumab, used with corticosteroids, confers mortality benefit, with the most consistent evidence in those on high-flow nasal cannula or mechanical ventilation.

I. Dosing: 8mg/kg rounded as below:
- 40 kg to 65 kg = 400mg
- 66 kg to 90 kg = 600mg
- > 90kg = 800mg

II. Tocilizumab should NOT be used in the following scenarios:
- Pregnancy or breast-feeding
- Suspected or confirmed bacterial, fungal, or viral infection other than SARS-CoV-2
- Active TB infection
- Hospitalization > 4 days
- Duration of mechanical ventilator > 24 hours

III. Approval: At UCHealth AMC, use of tocilizumab for COVID-19 treatment is restricted to Antimicrobial Stewardship and/or ID approval. Please send requests via secure chat to “AMC Antimicrobial Stewardship” group, or obtain ID consult.

IV. Notes
- Monitor for development of new, or re-activation of latent, infections

Convalescent Plasma

COVID-19 convalescent plasma is plasma obtained from donors who have previously recovered from COVID-19, and contains neutralizing antibodies to SARS-CoV-2. Convalescent plasma 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 bank (all units have high-titer neutralizing antibody) if use is desired outside of a clinical trial.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Evidence</th>
<th>Comments/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir (Veklury)</td>
<td>Nucleoside analog: inhibits viral RNA polymerase</td>
<td>In Vitro—low EC&lt;sub&gt;50&lt;/sub&gt; value = 0.77 μM [Lancet RCT vs. Placebo; ACTT-1 Results; Gilead brief] [FDA approval for hospitalized patients with COVID-19] [WHO conditionally recommends against use of remdesivir in hospitalized patients, regardless of disease severity based on lack of mortality benefit, and uncertainties in benefit in select populations] [In vitro data] suggest potential antagonism with concurrent hydroxychloroquine, avoid concurrent use. [Ackley, et al.] Multicenter, matched cohort showing remdesivir was not associated increased AKI in those with CrCl &lt; 30 compared to those &gt; 30 mL/min. [Davis et al.] showed 40% dialyzability and higher concentrations than non-HD patients at end of therapy; unclear clinical impact.</td>
<td>Consider use in patients requiring low O2, regardless of renal function. Lack of benefit observed in critical COVID-19 (i.e. mechanically ventilated or require high intensity O2), not recommended.</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory</td>
<td>RECOVERY Trial – RCT of Dexamethasone 6mg q24h x 10 days vs. supportive care alone: Recovery trial site; Medrxiv preprint</td>
<td>Based on substantial mortality benefit, use of dexamethasone 6mg daily (or equivalent dose of prednisone/methylprednisolone) should be considered if contraindications absent and patient on supplemental oxygen or mechanically ventilated. Alternatives may be considered if clinical indication for alternative. Patients who are discharged on home oxygen can be considered for up to 7 days total duration of therapy.</td>
</tr>
<tr>
<td>Tocilizumab and other IL-6 antagonists</td>
<td>IL-6 receptor antagonist [Theoretical management of patients with hyperinflammatory response (aka cytokine release)]</td>
<td>Case series (n=20), described rapid improvement in patients from oxygenation and inflammatory markers after 400mg dose. Only 2 patients were intubated at time. [Price et al. – Retrospective observational cohort of 153 tocilizumab patients, showed similar survival despite higher inflammatory markers than controls.] [Guaraldi et al. – Retrospective, observational cohort comparing 179 tocilizumab patients to 365 in the standard of care showed lower mortality and mechanical ventilatory in those treated with tocilizumab. Rates of new infections were 3 times higher.]</td>
<td>Low quality evidence, with high risk of bias, suggests tocilizumab is associated with improvements in inflammatory markers and mortality. Initial high quality clinical trials for IL-6 inhibitors, including the Roche sponsored and Regeneron sponsored studies, were terminated due to lack of benefit seen. Two recent trials, have suggested that tocilizumab provides mortality benefit when used in conjunction with corticosteroids, with the most consistent evidence in those on high-flow nasal cannula or mechanical ventilation.</td>
</tr>
<tr>
<td>Convalescent Plasma</td>
<td>Neutralizing SARS-CoV-2 specific IgG from recovered patients</td>
<td>Case series (n=20), described rapid improvement in patients from oxygenation and inflammatory markers after 400mg dose. Only 2 patients were intubated at time. [Price et al. – Retrospective observational cohort of 153 tocilizumab patients, showed similar survival despite higher inflammatory markers than controls.] [Guaraldi et al. – Retrospective, observational cohort comparing 179 tocilizumab patients to 365 in the standard of care showed lower mortality and mechanical ventilatory in those treated with tocilizumab. Rates of new infections were 3 times higher.]</td>
<td>Consider enrollment of patient into a convalescent plasma trial (PASSiton). EUA product can be ordered from blood bank if patient is not a candidate or does not wish to participate in clinical trial.</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>Janus kinase (Jak) inhibitor</td>
<td>FDA issues EUA for use with remdesivir for use in hospitalized patients with severe-critical COVID. [ACTT-2 Trial] identified baricitinb use with remdesivir led to a one day reduction in time to recovery compared to remdesivir alone. No survival benefit observed overall or in subgroup.</td>
<td>Baricitinib is not currently recommended for use in COVID-19 outside of a clinical trial given limited benefit over placebo for shortening time to recovery and no observed survival benefit.. Baricitinib is not currently available from wholesaler.</td>
</tr>
<tr>
<td>Bamlanivimab + Etesevimab</td>
<td>Monoclonal antibody directed against receptor binding domain of SARS-CoV-2 S protein.</td>
<td>BLAZE-3 Trial shows accelerate decline in viral load with combination BAM+ETE.</td>
<td>FDA issues EUA for BAM +ETE for use in patients with mild-moderate COVID at high risk of progression to severe disease.</td>
</tr>
<tr>
<td>Bamlanivimab (LY-CoV555)</td>
<td>Monoclonal antibody directed against receptor binding domain of SARS-CoV-2 S protein.</td>
<td>FDA issues EUA for Bamlanivimab for use in patients with mild-moderate COVID at high risk of progression to severe disease.</td>
<td>Chen, et al. 2020 – Interim Analysis of Phase 2 RCT, demonstrated that one dosing regimen (2,800 mg) accelerated natural decline in viral load, and all three dosing regimens (700 mg, 2800 mg, 7000 mg) had lower rates of hospitalization at day 11 (1.6% vs 6.3).</td>
</tr>
<tr>
<td>Casirivimab/Imdevimab (REGN-COV2) Antibody Cocktail</td>
<td>Monoclonal antibody directed against receptor binding domain of SARS-CoV-2 S protein.</td>
<td>Weinreich et al. – outpatient RCT (n=275); Decrease in viral load from day 1-7 in seronegative patient, numerically lower medical visits.</td>
<td>FDA issues EUA for REGN-COV2 for use in patients with mild-moderate COVID at high risk of progression to severe disease. Regeneron press release – Treatment with REGN-COV2 reduced COVID-19 related medical visits by 57% through day 29 (2.8% combined dose groups; 6.5% placebo; p=0.024); n = 799. Treatment with REGN-COV2 reduced COVID-19 related medical visits by 72% in patients with one or more risk factor.</td>
</tr>
<tr>
<td>ACE-1 / ARB</td>
<td>Anti-hypertensives</td>
<td>Theoretical increased viral entry through animal models showing RAAS inhibition leads to ACE-2 upregulation. No evidence to date of a strong association.</td>
<td>Kassiri et al. ACE2 knockout mice have adverse ventricular remodeling</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Anit-inflammatory, analgesic, anti-pyretic</td>
<td>Uncontrolled case report of 4 patients taking ibuprofen who had worsening infection and theoretical upregulation of ACE-2 receptors (target for viral entry). No strong evidence to avoid NSAIDs for fever/analgiesia in COVID-19 patients.</td>
<td></td>
</tr>
</tbody>
</table>
| Ruxolitinib, acalabrutinib, other TKIs | Janus kinase (Jak) inhibitor AAK1 inhibition impacting viral entry and anti-inflammatory | Theoretical, no published clinical evidence available presently. Ruxolitinib pilot RCT results Acalabrutinib 19 patient observational report | | | Insufficient evidence to recommend use presently outside of clinical trial.
<table>
<thead>
<tr>
<th>IVIG</th>
<th>Neutralizing antibodies, immunomodulating effects</th>
<th>Cao et al. case report, n=3</th>
<th>Presence of neutralizing antibodies not expected, theoretical immunomodulating effects. <strong>SCCM guidelines</strong> recommend against use.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Pleiotropic, immunomodulating effects, cardioprotective</td>
<td>No published evidence, based on mechanism and extrapolation from other data</td>
<td>Not routinely recommended, consider adding/continuing if other compelling indication exists for statin.</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>RNA polymerase inhibitor</td>
<td><strong>In Vitro</strong> EC50 higher then remdesivir and CLQ/HCLQ.</td>
<td>Favipiravir is under investigation, but is not approved for use in the U.S., and no active study sites listed in U.S.</td>
</tr>
<tr>
<td>Zinc</td>
<td>Unclear, inhibits viral replication</td>
<td>No published studies, theoretical</td>
<td>Recommend against routine use</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Unclear, likely immunomodulating</td>
<td>No published evidence, ongoing high-dose IV study in China</td>
<td>Low quality evidence, recommend against routine use</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Anti-inflammatory, reduces the production of active IL-1β</td>
<td><strong>Deftereos et al.</strong> Open-label, randomized clinical trial, n = 105, 55 colchicine, 50 control <strong>COLCORONA Preprint</strong> - RCT comparing colchicine (0.5 mg BID x3 days and daily thereafter) to placebo. No significant mortality benefit or decrease in need for MV; small decrease in the need for hospitalization (4.5% vs. 5.9%, p = 0.04). No difference in serious ADE’s but significantly higher incidence of any related ADE with colchicine (24.2% vs. 15.5%, p &lt; 0.0001, NNH = 12)</td>
<td>Pilot study showed potential benefit of colchicine. Not currently recommended outside the context of a clinical trial given the limited evidence of efficacy and evidence of potential harm.</td>
</tr>
<tr>
<td>Interferon</td>
<td>Direct viral effects and indirect stimulation of innate immune responses against viral infection</td>
<td><strong>SOLIDARITY RCT</strong> - regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients. Mostly reports of combination use with ribavirin or LPV/r from China. <strong>INTEREST</strong> trial—INF 11b had no effect on mortality in ARDS, but increased mortality in subgroup when used w/ steroids</td>
<td>No direct comparison studies in SARS-CoV-2. <strong>SCCM guidelines</strong> do not recommend.</td>
</tr>
<tr>
<td>Hydroxychloroquine (HCLQ)/Chloroquine (CLQ)</td>
<td>Anti-inflammatory and inhibition of viral entry</td>
<td><strong>In Vitro</strong>—HCLQ EC50 = 0.72 μM &amp; CLQ EC50 = 5.47 μM</td>
<td>Multiple negative studies among hospitalized patients and those for secondary prophylaxis. <strong>Hydroxychloroquine is not recommended for use.</strong></td>
</tr>
<tr>
<td>HIV Protease Inhibitors:</td>
<td>Inhibition of viral protease</td>
<td><strong>LPV/r</strong>: in vitro extrapolated from SARS-CoV-1 and MERS-CoV. · Chu-2004 and Chan-2003 retrospective SARS-CoV-1 · NEJM prospective study of LPV/r vs. supportive care - DRV/c—Janssen, found no relevant in vitro activity · ATV—no in vitro studies, but reports that models show high affinity for docking</td>
<td><strong>SOLIDARITY</strong> showed no benefit of LPV/r in severe and critical COVID-19. <strong>NEJM</strong> study vs. supportive care showed no benefit, though small and most started on therapy later in illness. Presently lack of evidence for benefit, do not use outside of clinical trials.</td>
</tr>
<tr>
<td>Ribavirin (RBV)</td>
<td>Nucleoside analog: inhibits viral RNA polymerase</td>
<td>In vitro EC50 = 109.5 μM</td>
<td>Not recommended as current there are no evidence for use. Use with caution given safety (anemia, teratogenicity). Enteral route preferred.</td>
</tr>
<tr>
<td>Nitazoxanide (NTZ)</td>
<td>Unclear, potentially interaction with host regulated pathways</td>
<td>In vitro only, EC50 = 2.12 μM</td>
<td>Insufficient evidence for routine use, outside of a clinical trial</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Antibacterial and proposed anti-inflammatory effects</td>
<td>No in vitro antiviral effects</td>
<td>Low quality evidence. Combination not recommended outside concern for atypical pneumonia. Monitor QTc closely. Not recommended for use</td>
</tr>
</tbody>
</table>

**Data is rapidly evolving with therapeutics for COVID-19 and recommendations are subject to change. Please refrain from re-posting and printing this document.**

Green denotes therapies with moderate to strong clinical evidence for use and guidelines recommend use; Yellow denotes limited evidence and may prove beneficial, though not recommended outside clinical trial; Red denotes evidence available showing therapies are not effective and/or potentially harmful and thus should not be used in clinical practice.

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University of Colorado Hospital / University of Colorado Health
Anticoagulation Subcommittee

ANTICOAGULATION RECOMMENDATIONS FOR HOSPITALIZED COVID-19 PATIENTS

I. General Information
• Patients infected with the COVID-19 virus are potentially at increased risk of both venous thromboembolism and micro thrombosis in multiple vascular beds, due to hospitalization, immobilization/isolation, and the thrombo-inflammatory state generated by COVID-19 infection itself
• COVID-19 has been associated with a coagulopathic presentation that when severe can mimic DIC. Coagulopathy typically increases thrombosis and not bleeding
• Lab derangements may include elevated d-dimers, prolonged prothrombin time ratios, elevated fibrinogen, elevated ferritin and thrombocytopenia

II. Recommendations for Subcutaneous VTE Prophylaxis

<table>
<thead>
<tr>
<th>Floor Patients</th>
<th>D-dimer &lt;1500* AND</th>
<th>D-dimer &gt; 1500* OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 70k</td>
<td>TEG (MA) &gt; 70k</td>
</tr>
<tr>
<td>(Only if available, see info below)</td>
<td>(Only if available, see info below)</td>
<td></td>
</tr>
<tr>
<td>Weight &lt;100 kg</td>
<td>Enoxaparin 40 mg once daily</td>
<td>Enoxaparin 30 mg BID</td>
</tr>
<tr>
<td>Weight 100-150 kg</td>
<td>Enoxaparin 30 mg BID</td>
<td>Enoxaparin 40 mg BID</td>
</tr>
<tr>
<td>Weight &gt; 150 kg</td>
<td>Enoxaparin 40 mg BID</td>
<td>Enoxaparin 0.5 mg/kg BID</td>
</tr>
<tr>
<td>AKI (GFR&lt;30 ml/min)#</td>
<td>UFH 5000 U TID</td>
<td>UFH 7500 U TID</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU Patients</th>
<th>D-dimer &lt;1500* AND</th>
<th>D-dimer &gt; 1500* OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 0k</td>
<td>TEG (MA) &gt; 0k</td>
</tr>
<tr>
<td>(Only if available, see info below)</td>
<td>(Only if available, see info below)</td>
<td></td>
</tr>
<tr>
<td>Weight &lt;100 kg</td>
<td>Enoxaparin 40 mg once daily</td>
<td>Enoxaparin 40 mg BID</td>
</tr>
<tr>
<td>Weight 100-150 kg</td>
<td>Enoxaparin 40 mg BID</td>
<td>Enoxaparin 0.5 mg/kg BID</td>
</tr>
<tr>
<td>Weight &gt; 150 kg</td>
<td>Enoxaparin 60 mg BID</td>
<td>Enoxaparin 0.5 mg/kg BID</td>
</tr>
<tr>
<td>AKI (GFR&lt;30 ml/min)#</td>
<td>UFH 5000 U TID</td>
<td>UFH 7500 U TID</td>
</tr>
</tbody>
</table>

* Based on scarce available mortality data and preliminary data from anti-Xa activity levels in UCH pts

& This guideline does not endorse performing Thromboelastography (TEG) to be routinely done in COVID-19 patients, particularly those on the floor, but use of results may be considered if it is performed. Available in data from other populations indicate hypercoagulability is present in patients with TEG MA values above 70, although no outcomes data in COVID-19 to date. In addition, no clear data to date to incorporate other markers of inflammation like fibrinogen or ferritin at this time to drive anticoagulation choices, but these have been noted to be elevated in severely sick COVID-19 patients

# Considerations for patients with AKI:
• Patients on renal replacement therapy (HD, CRRT) may require more aggressive anticoagulation therapy in order to prevent clotting of the filter. Renal service should be consulted for final recommendation.
• Estimated GFR should not be used alone to assess renal function as patients with AKI may still have estimated GFR > 30 ml/min.
III. Additional Considerations for Prophylactic or Therapeutic Anticoagulation in COVID-19 Patients.

a. COVID-19 patients with a *history of thromboembolic disease and/or on chronic anticoagulation prior to admit* should continue home anticoagulation regimen if clinically appropriate, or transition to alternative agent (most cases IV UFH) for therapeutic anticoagulation.

b. COVID-19 patients who develop *new arterial or venous thromboembolic events* should be treated with therapeutic anticoagulation (UFH, LMWH) as standard of practice would dictate.

c. **For high clinical suspicion of new thromboembolic events**, consider empiric therapeutic anticoagulation using heparin gtt and order a truncated, lower extremity DVT protocol (POCUS) as a confirmatory test.
   i. Initiation of therapeutic anticoagulation without confirmed or high clinical suspicion of DVT/PE, is controversial and is **not** recommended by *national/international guidelines (see below)*
   ii. In the setting of extremely high D-dimers (e.g. >3000 ng/ml), persistent clotting of lines and/or worsening clinical course, therapeutic anticoagulation may be considered and a multidisciplinary discussion with critical care attending, anti-thrombosis services and others (path, heme) is recommended.

d. Primary teams are recommended to consult the inpatient anticoagulation service (metro) or pharmacy (North and South) to *assist with dose optimization* (AKI, drug-drug interactions, extremes of body weight, other) or **therapeutic selection** (appropriate heparin order set, use of alternative anticoagulants such as DOACS or injectable DTIs). Issues include:
   i. For Enoxaparin: measure anti-Xa level 4 hours after 3rd dose. Goal = 0.3-0.5. Increase dose as needed guided by anti-Xa level. Consider using TEG.
   ii. When TEG monitoring available: Use Kaolin / heparinase.

IV. **Available Guidance on Anticoagulation is available through the following organizations**

a. International Society of Thrombosis and Haemostasis
b. American Society of Hematology c
   Anticoagulation Forum
   American College of Cardiology
# Remdesivir in Renal Dysfunction

## Background
- Remdesivir (RDV) is FDA approved for the treatment of COVID-19 in adults with confirmed COVID-19 requiring hospitalization.
- Clinical studies primarily show benefit in patients requiring supplemental oxygen, whereas patients requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and/or ECMO are unlikely to benefit.
- Limited data exists regarding use in patients with renal dysfunction due to exclusion of patients with eGFR < 30 ml/min in clinical trials, while the package insert suggests avoiding use in those with renal impairment.

## Concerns for Renal Accumulation
- RDV is metabolized to an active prodrug (GS-443902) and an inactive prodrug (GS-441524).
- RDV has limited water solubility and is therefore formulated with the solubilizing agent sulfobutylether-β-cyclodextrin (SBECD).
- Accumulation of SBECD in animals at doses 50-fold greater than administered to humans has been associated with liver necrosis/renal tubule obstruction, leading to concerns for acute nephrotoxicity.
- Decreasing renal function causes reduced SBECD clearance and increased exposures, but SBECD exhibits good safety and tolerability in humans.
- Further, SBECD is readily removed by continuous RRT and hemodialysis, and significant accumulation only occurs in patients when dialysis is held for prolonged periods.
- As 49% of RDV is recovered in urine as GS-441524, drug accumulation is possible in renal dysfunction, concerning for...

## Table 1: Clinical Studies of RDV in varying degrees of renal function

<table>
<thead>
<tr>
<th>Study (No. patients)</th>
<th>Design</th>
<th>Population</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ackley et al. (n=347)</td>
<td>Multicenter, retrospective cohort</td>
<td>CrCl ≥ 30 (n = 307 ), CrCl &lt; 30 (n = 40); patients with CrCl &lt; 30 were older, had more comorbidities and more likely to have AKI, vasopressor use, and be mechanically ventilated.</td>
<td>No difference was detected in peak Scr or at end of therapy, AKI at 48 hours post treatment, and no different in ALT ≥ 5 ULN or discontinuation due to LFT abnormalities</td>
</tr>
<tr>
<td>Aiswarya et al. (n=48)</td>
<td>Single center, prospective observational study</td>
<td>Patients on HD (n = 48), given RDV 100 mg 4 hours prior to HD</td>
<td>There were no events of significant LFT alteration with administration of 2-6 doses of RDV.</td>
</tr>
<tr>
<td>Estiverne et al. (n=18)</td>
<td>Single center, retrospective, observational cohort study</td>
<td>AKI on RRT (n=3); ESRD (n=2), AKI (n = 5); GFR &lt; 30 (n=8)</td>
<td>2 patients developed ALT &gt; 5 ULN, both attributed to shock. 3 cases of LFT derangement (2 grade 1, 1 grade 2) potentially related to RDV. Eight of 13 not requiring RRT had improvement in Scr, 5 worsened. One case of worsening Scr possibly related to RDV.</td>
</tr>
<tr>
<td>Davis et al. (n=2)</td>
<td>Pharmacokinetic study</td>
<td>2 patients on HD</td>
<td>RDV plasma half-lives were doubled but concentrations were not elevated compared with reference data. GS-441524 concentrations were 3–4.5-fold higher.</td>
</tr>
</tbody>
</table>

## Conclusions
- Several clinical studies have evaluated the use of RDV in patients with renal dysfunction and hemodialysis.
- Likely owing to the small amount of cyclodextrin and short duration of exposure, available clinical studies suggests no increase in safety events in patients with renal dysfunction.
- Consequently, RDV should be used in patients with a clinical indication, without regard to renal function. Liver function tests should be monitored frequently while on RDV.
- Any suspected adverse drug reactions should be reported via RL solutions.
What are COVID-19 Monoclonal Antibodies?
COVID-19 monoclonal antibodies (mAbs) are laboratory-made neutralizing antibodies against SARS-CoV. Currently available products bind to the virus spike protein to prevent their interaction with human cells. Several mAb products have received FDA emergency use authorization (EUA) for use among ambulatory patients with mild-moderate COVID-19 who are at high risk for developing severe disease. mAbs have been studied alone and in combination and continue to be under active investigation. mAbs that have received EUA are:

- Bamlanivimab (Eli Lilly)
- Casirivimab/imdevimab (Regeneron)
- Bamlanivimab/etesevimab (Eli Lilly)

Evidence for Effectiveness and Safety

**Bamlanivimab (BAM)**
Phase 2 double-blind RCT (BLAZE-1, Chen et al, 2020)
- BAM vs placebo given to 452 outpatients with mild-moderate COVID-19, within median 4 days after symptom onset
- Primary endpoint: non-significant decrease in viral load at day 11 with BAM vs placebo
- Secondary outcome: fewer admissions and ER visits at day 29 with BAM (5/309, 2%) vs placebo (9/143, 6%)
- Decreased symptoms with BAM vs placebo on day 2-6
- No serious safety events

**Casirivimab/imdevimab (CAS/IMD)**
Phase 2 double-blind RCT (Weinreich et al, 2021)
- CAS/IMD vs placebo given to 275 outpatients with symptomatic non-severe COVID-19 within 7 days of symptom onset and 72 hrs of PCR test
- Primary endpoint: decreased overall viral load at 7 days with CAS/IMD vs placebo
- Secondary outcome: decreased need for medical visits at 29 days with CAS/IMD (6/182, 3%) vs placebo (6/93, 6%)
- No overall difference in adverse events between CAS/IMD vs placebo; one reported anaphylactic reaction in CAS/IMD recipient.

**Bamlanivimab/etesevimab (BAM/ETE)**

BLAZE-1 Phase 2 double-blind RCT (Gottlieb et al, 2021)
- Primary outcome: significant decrease in viral load at day 11 with BAM/ETE vs placebo
- Secondary outcome: Decreased need for hospitalization or ER visit with BAM/ETE (1/112, 1%) vs placebo (9/156, 6%)

BLAZE-1 Phase 3 RCT
- BAM/ETE vs placebo given to 1035 patients meeting high-risk criteria for progressing to severe disease
- Primary endpoint: significant decrease in COVID-19 related hospitalization and death at day 29 with BAM/ETE (11/518, 2%) vs placebo (36/517, 7%); all 10 deaths occurred in placebo group.

**Important Notes:**
- mAbs are not FDA-approved products and not considered standard of care; clinical judgment and shared, informed decision-making should be exercised when considering use for individual patients
- NIH panel recommends bamlanivimab + etesevimab for patients meeting EUA criteria, based on phase 3 clinical trial data (unpublished) demonstrating decreased incidence of hospitalization or death (23 Feb 2021)
- mAb combinations are preferred over single mAb products for likely improved efficacy and decreased potential for resistant mutants. Based on mAb activity against currently circulating SARS-CoV-2 variants, *casirivimab/imdevimab is the preferred mAb product at UCH*. Other products may be used if CAS/IMD is not available.
- mAbs may be considered for patients who meet the above criteria but are hospitalized for another reason (i.e., are not hospitalized due to COVID-19); at AMC please send inpatient requests via secure chat to “AMC 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.
**Criteria for mAb Use**

COVID-19 mAbs can be given under EUA to adults and children aged ≥12 years and weighing at least 40kg with mild-moderate COVID-19, who are at high risk for progression to severe disease, and in whom treatment can be given within 10 days of symptom onset.

**Dosing and Administration**

- **Dosing:**
  - BAM: 700mg IV x 1 dose
  - CAS/IMD: 2,400mg IV x 1 dose
  - BAM/ETE: 700/1400mg IV x 1 dose

- **All infusions are given over 1 hour, followed by at least 1 hour observation post-infusion. Patients should anticipate a total appointment time of about 3 hours.**
- **No adjustments needed for kidney or liver impairment.**
- **Note:** Currently the medication is provided at no cost; however, infusion facility fees may apply.

**How to Order: Provider Instructions**

- **A random allocation process is used to ensure equitable medication access in the event of a medication shortage. Please see schematic of the process on page 4.**
- **After an informed discussion with the patient, including reviewing the FDA EUA fact sheets for Providers and for Patients, Parents, and Caregivers (available online), follow the steps below to obtain the medication for the patient:**
  1. Enter patient information into the Colorado statewide random allocation system:
     - [https://redcap.link/COVIDMedsAllocationTool](https://redcap.link/COVIDMedsAllocationTool)
  2. After completing the form you will be notified immediately if your patient has been selected to receive mAb treatment.
  3. Select the preferred infusion site within the online form. See a map of active infusion sites in Colorado here:
  4. Send a medication order to the selected infusion site via the standard IV infusion order process for that site. Note that each facility may have different policies regarding accepting medication orders from providers outside the healthcare system, infusing pediatric patients, etc. Please contact facilities directly to confirm details.
     - UCHealth Epic users: Enter a Therapy Plan for “COVID OUTPATIENT MONOCLONAL INFUSION OIC”; see attached instructions.
     - Providers outside of UCHealth or who do not use Epic may send infusion orders using the attached Order Form, faxed to the appropriate location.
  5. After receiving the medication order, the infusion site will contact the patient directly to schedule the infusion, and provide the patient with instructions for their appointment.
Important Information To Discuss With Patients

- COVID-19 monoclonal antibodies are not FDA-approved and are not considered standard of care, but when given early in the course of infection, may improve symptoms and prevent the need for hospitalization in patients who are at high-risk for developing severe disease.
- In preliminary studies, these medications were overall well-tolerated and seemed to be safe. The most common side effects were nausea, diarrhea, and dizziness. More serious adverse events are possible (e.g. anaphylaxis).
- Patients may be declined the infusion if by the time of their appointment:
  - They are hypoxic and require supplemental oxygen, and/or otherwise hemodynamically unstable,
  - There is no remaining supply,
  - More than 10 days have passed their symptoms started.
- Whether or not patients receive the infusion, they should continue isolation procedures and supportive measures at home, and report any new or worsening symptoms.

Adverse Event Reporting

- The prescribing health care provider (and/or the provider’s designee) is responsible for mandatory reporting of all medication errors and serious adverse events potentially related to mAb treatment within 7 days from the onset of the event.
- Events may be reported via RL Solutions (within UCHealth system) or directly to FDA Medwatch http://www.fda.gov/medwatch/report.htm

FAQs

- Can selection by the random allocation system be transferrable to others (e.g. family members)? No, selection is for individual patients only.
- If my patient cannot be scheduled at their preferred infusion site, can they try to be scheduled at another infusion site? Yes, they can contact another infusion site and inquire about availability.
- Are pregnant patients eligible? Pregnant patients were excluded from clinical trials, so there are no data on safety or efficacy in this population. However, potential risks and benefits should be discussed with individual patients.
- Can patients who are hospitalized for another reason but who tested positive for COVID-19 get a monoclonal antibody? Yes, mAbs may be considered for patients who meet the EUA criteria but who are hospitalized for another reason (i.e., are not hospitalized due to COVID-19); however, policies for inpatient mAb infusions may vary by site.
UCHealth Monoclonal Antibody Infusion Process

Patient Tests Positive for COVID-19

Provider Evaluation
- Provider ensures patient meets EUA criteria and decides patient is appropriate to receive medication
- Provider discusses EUA fact sheet with patient

Patient chooses to pursue EUA product

Provider Enters Patient Information into CDPHE Random Allocation Tool

Real-time Random Allocation Result
- Eligible and Selected
- Ineligible or Not Selected

Provider Places Medication Order to Infusion Center
- UCH provider: Enter Therapy Plan in EPIC (see attached instructions)
- Non-UCH provider: Fax paper orders to OIC (see attached order form)

Infusion Center Receives Order
- Confirms patient selection random allocation with email
- Contacts patient to schedule

Infusion Appointment (~3 hours)
- Patient arrives masked and follows site-specific instructions
- Vital Signs/SpO2 assessed before infusion
- Monoclonal infusion (1-hr)
- Post-infusion observation (1-hr)

Follow-up
- Patient should have follow-up encounter with ordering provider 1-2 weeks after infusion, or sooner as needed

Unstable Vitals or SpO2 < 90%

Patient is counseled regarding routine isolation and supportive care measures

Monoclonal not given, patient sent to the ED for evaluation
Epic Therapy Plan Infusion Order Instructions

1. Within the patient visit, select Therapy Plan in header (see screenshot below)
2. Search “COVID OUTPATIENT MONOCLONAL INFUSION OIC”
3. Associate with correct diagnosis
4. Plan start date is today
5. Select corresponding treatment department
   a. North Region: PVH Infusion OP
   b. South Region: MHC Infusion OP
   c. Denver/Metro Region: AMC CTRC Infusion Unit
6. Select Assign Plan
7. Do not uncheck any orders or change timing
8. Dosing is defaulted, please answer order questions accordingly
9. Accept and Sign Plan