SARS-CoV-2 (COVID-19) positive or strongly suspected

**General Considerations:**
- Optimize supportive care based on clinical status
- Avoid corticosteroids unless indicated for separate comorbidity (e.g., septic shock, COPD, asthma, ARDS, etc.) - limited evidence exists for adjunctive corticosteroids and results are mixed
- Consider VTE Prophylaxis (see UCH COVID-19 Anticoag Recommendations)
- Consider empiric antibiotics for concurrent bacterial pneumonia (CAP or HAP/VAP) according to clinical suspicion, with de-escalation or discontinuation of antibiotics if subsequent work-up indicates low likelihood of bacterial infection (negative cultures, low procalcitonin < 0.5, etc.)

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**Mild Disease**
- No hypoxia or radiographic evidence of pneumonia

**Moderate Disease, or Mild Disease with risk factors for complications and/or progression**
- Moderate disease: hypoxia and/or radiographic evidence of pneumonia
- Risk factors for complications/progression: age ≥ 65 years, heart disease, lung disease, diabetes, transplant, immunocompromised state, obesity

**Severe Disease**
- Requiring high-flow oxygen, non-invasive or mechanical ventilation
- Evidence of hyperinflammatory response

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**Isolate at home**
- Supportive care measures (hydrate, symptomatic care for fever, cough, etc.)
- Avoid steroids unless indicated for other conditions (e.g. COPD exacerbation)
- Monitor for progressive or worsening symptoms

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**There are currently no FDA approved treatments for COVID-19.**

Based on preliminary results from a randomized clinical trial, remdesivir has been granted emergency use authorization (EUA) by the FDA, and is currently recommended by the NIH for treatment of severe COVID-19 (not recommended for mild-moderate disease).

- UCHealth has received a small allocation of EUA remdesivir, see criteria below for consideration.
- Compassionate use of remdesivir remains available for patients who are pregnant or <18 years old (though this is expected to be phased out over time)

Other off-label therapies are not routinely recommended outside of a clinical trial, and patients should access other potential treatments via clinical trials, when available.

Attatched pages list proposed agents as well as details about use and links to available studies if use is considered.

Studies available at Anschutz Campus:
- Hydroxychloroquine placebo-controlled trial (ORCHID trial)
- Remdesivir moderate disease open-label study (Gilead)
- Sarilumab placebo-controlled trial (Regeneron)
- Convalescent plasma open-label study (investigator initiated, available at all UCHealth hospitals)
- Fibrinolytic therapy (tPA) randomized controlled trial

Continue work-up for potential concurrent infection. Empiric antibacterial therapy should be de-escalated or discontinued if subsequent work-up indicates no or low likelihood of bacterial infection (negative cultures, low procalcitonin < 0.5, etc.).

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**UCHealth specialty consultation for pharmacotherapy**

*Metro:* ID consult required if considering pharmacotherapy; ensure that patient (or POA) is interested in investigational therapies prior to consulting.

*South:* Any experimental therapy used off-label with the exception of hydroxychloroquine or tocilizumab should be discussed with ID, pulmonary/critical care, or pharmacy

*North:* Contact ID or pulmonology for guidance.

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Please view these links for national society guidelines on COVID-19 therapeutics:
1. [Infectious Diseases Society of America](#)
2. [National Institute of Health](#)
3. [Society of Critical Care Medicine](#)
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Evidence</th>
<th>Comments/Recommendation</th>
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<tbody>
<tr>
<td>Remdesivir</td>
<td>Nucleoside analog: inhibits viral RNA polymerase</td>
<td><em>In Vitro</em>—low EC$_{50}$ value = 0.77 μM</td>
<td>Investigational antiviral, access via clinical trial or expanded access program only. Compassionate use still supported for pregnant patients and pediatrics (&lt; 18yr)</td>
</tr>
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<td><em>Lancet RCT vs. Placebo; NIH briefing of ACTT study; Gilead brief</em></td>
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<tr>
<td>Hydroxychloroquine</td>
<td>Anti-inflammatory and inhibition of viral entry</td>
<td><em>In Vitro</em>—HCLQ EC$<em>{50}$ = 0.72 μM &amp; CLQ EC$</em>{50}$ = 5.47 μM</td>
<td>Unclear role, evidence published to date is mixed and study designs are not highest quality. Current use outside of a clinical trial should be weighed against risk for adverse events and unclear benefit for COVID-19 infection.</td>
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<tr>
<td>(HCLQ)/Chloroquine (CLQ)</td>
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<td>HIV Protease Inhibitors:</td>
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<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>Inhibition of viral protease</td>
<td>*LPV/r: in vitro activity extrapolated from SARS-CoV-1 and MERS-CoV.</td>
<td>Role unclear for us in COVID-19. NEJM study vs. supportive care showed no benefit, though small and most started on therapy later in illness. Presently unclear role, and might be an alternative if other options unavailable due to supply or contraindications/intolerance.</td>
</tr>
<tr>
<td>Atazanavir (ATV)</td>
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<td><em>NEJM</em> prospective study of LPV/r vs. supportive care for SARS-CoV-2.</td>
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<tr>
<td>Nitazoxanide (NTZ)</td>
<td>Unclear, potentially interaction with host regulated pathways</td>
<td><em>ATV—no in vitro studies, but reports that models show high affinity for docking</em></td>
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</tr>
<tr>
<td>ACE-I / ARB</td>
<td>Anti-hypertensives</td>
<td><em>Theoretical</em> increased viral entry through animal models showing RAAS inhibition leads to ACE-2 upregulation. No evidence to date of a strong association.</td>
<td>ACC, AHA, and others recommend continuation of these meds in setting of COVID-19 infection, as abrupt discontinuation can worsen underlying conditions that have proven mortality benefit.</td>
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<tr>
<td></td>
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<td><em>Kassiri et al. ACE2 knockout mice have adverse ventricular remodeling</em></td>
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<tr>
<td>NSAIDs</td>
<td>Anit-inflammatory, analgesic, anti-pyretic</td>
<td><em>Uncontrolled case report of 4 patients</em> 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/analgesia in COVID-19 patients.</td>
<td>EMA, FDA and WHO do not recommend to avoid NSAIDs due to concerns about worse outcomes in COVID-19. Use APAP or NSAID as indicated based on underlying comorbid conditions. Do not stop low-dose Aspirin for cardiovascular benefit.</td>
</tr>
<tr>
<td></td>
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<td><em>Oudit et al. ACE-2 downregulation associated with myocardial dysfunction during SARS-CoV-1</em></td>
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<td></td>
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<td><em>Zhang P, et al. Retrospective analysis of ACEI/ARB use</em></td>
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<tr>
<td>Therapy</td>
<td>Category</td>
<td>Summary</td>
<td>Evidence</td>
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<tr>
<td>Corticosteroids</td>
<td>Anti-inflammatory</td>
<td>Mixed—some instances of delayed viral clearance (indifference/worse outcomes—extrapolated from SARS-CoV-1, MERS, influenza, RSV) to improved survival among those with ARDS.</td>
<td>Evidence weak regarding corticosteroid administration. Routine use recommended against by CDC and WHO. SCCM guidelines provided weak recommendations to consider in refractory shock and/or ARDS.</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6 receptor antagonist</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.</td>
<td>Low quality evidence with improvement. Concerns with safety, particularly with worsening of infections (TB, fungal, other bacterial) due to immunosuppressive characteristics. Criteria for off-label prescribing for COVID-19 on page 11.</td>
</tr>
<tr>
<td>Sarilumab</td>
<td>IL-6 antagonist</td>
<td>None, clinical trials underway</td>
<td>Similar considerations to tocilizumab.</td>
</tr>
<tr>
<td>Baricitinib &amp; other Jak-I’s</td>
<td>Janus kinase (Jak) inhibitor</td>
<td>Theoretical, no clinical evidence available presently.</td>
<td>Not recommended given limited evidence and theoretical mechanisms.</td>
</tr>
<tr>
<td>IVIG</td>
<td>Neutralizing antibodies, immunomodulating effects</td>
<td>Cao et al. case report, n=3</td>
<td>Presence of neutralizing antibodies not expected, theoretical immunomodulating effects. Not routinely recommended. SCCM guidelines recommend against use.</td>
</tr>
<tr>
<td>Interferon</td>
<td>Direct viral effects and indirect stimulation of innate immune responses against viral infection</td>
<td>Mostly reports of combination use with ribavirin or LPV/r from China. INTEREST trial—INF β1b had no effect on mortality in ARDS, but increased mortality in subgroup when combined with steroids.</td>
<td>No direct comparison studies in SARS-CoV-2. Recommend against routine use. SCCM guidelines do not recommend.</td>
</tr>
<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>In Vitro 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>Azithromycin</td>
<td>Antibacterial and proposed anti-inflammatory effects</td>
<td>Low quality evidence. Combination not recommended outside concern for atypical pneumonia. Monitor QTc closely.</td>
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</tbody>
</table>

*There are currently no FDA approved agents for the treatment of COVID-19, and limited evidence supports clinical benefit; weigh risks and benefits prior to initiation. Data is rapidly evolving with therapeutics for COVID-19 and recommendations are subject to change. Please refrain from re-posting and printing this document.*
## Remdesivir: Compassionate Use via Gilead

**Eligibility Criteria:**
- Hospitalized with confirmed SARS-CoV2 by polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with coronavirus disease (COVID-19) with PCR pending
- Pregnant or < 18 years of age
- Adequate renal function with estimated glomerular filtration rate (eGFR) ≥ 30 ml/min by local laboratory measure
- Alanine aminotransferase (ALT) ≤ 5 x upper limit of normal (ULN) by local laboratory measure

## Remdesivir: FDA Emergency Use Authorization (EUA)

Based on preliminary results from a randomized clinical trial, remdesivir has been granted FDA emergency use authorization (EUA) for patients with severe COVID-19. A small allocation has been made available to UCHealth. Criteria for use and other considerations are below. Criteria are subject to change depending on supply and demand.

### Restrictions for use:
- Confirmed COVID-19 positive
- Duration of symptoms ≤ 10 days (longer symptom duration allowed if transplant recipient or other severely immunocompromised host)
- Radiographic evidence of pneumonia
- Requiring ≥ 4L O2, NIV, or mechanical ventilation
- ALT < 5x ULN
- Creatinine Clearance ≥ 30 mL/min or receiving CRRT (SBEC present in remdesivir is expected to be adequately removed by CRRT)
- ID consultation (AMC location only)

### Considerations for prescribing:
- Dosing: 200mg IV once on day 1, followed by 100mg IV q24h on days 2-5
- Touch base with pharmacy to determine availability given limited supply available
- Prior remdesivir receipt as part of clinical trials should not be considered for EUA supply
- If patient is already showing signs of clinical improvement or is unlikely to survive in the immediate short-term such that remdesivir use is unlikely to change clinical outcome, please do not consider EUA use
- Treatment courses will be for a max of 5 days, but courses may be shortened in the event patient improves and is ready for discharge prior to completing 5 days of treatment.
- Prescribers must read [FDA Fact Sheet](#) and patients/family should be provided with [patient focused FDA fact sheet](#) for review and any questions addressed prior to ordering. Patient/Family should understand risk/benefits and agree to EUA remdesivir use before being prescribed the medication.
- All adverse drug reactions (including death) must be reported ASAP via RL Solutions (do not report directly to FDA MedWatch)

## Convalescent plasma

Convalescent plasma is available at UCHealth hospitals via enrollment in ongoing multi-center open-label study, with product obtained using FDA expanded access protocol. Eligibility based on disease severity and product availability. Contact site study coordinator for patient referral.
**Tocilizumab: System Criteria for Use**

- Confirmed COVID-19 positive (No empiric use)
- Critical illness associated with COVID-19 evidenced by: Respiratory failure requiring mechanical ventilation or Shock or failure of other organs requiring ICU care
- Evidence of ≥2 laboratory abnormalities associated with hyperinflammatory response: D-Dimer > 1 mcg/mL, Serum ferritin > 600 mcg/L, Persistent fever > 38.3°C, C-Reactive Protein > 100 mg/L or 10x ULN, Interleukin-6 ≥ 3x ULN
- Ordered/recommended by Infectious Diseases or Pulmonology Services
- Review and approval by secondary provider(s) not directly involved in the patients care
- ALT/AST < 5x ULN
- Platelet Count is ≥ 50,000/mm3
- Absolute Neutrophil Count (ANC) is ≥ 500/mm3
- No presence of active or strongly suspected bacterial or fungal infection. Stability of these infections with appropriate antibiotics/antifungals and proceeding with tocilizumab should be carefully weighed by ordering/consulting infectious diseases and/or pulmonology physician.
- Consider avoiding use for significantly elevated procalcitonin levels (i.e. > 2 ng/mL), as this may represent an active bacterial infection
- No history of untreated or inadequately treated TB, or latent TB infection
- Caution if high risk of GI perforation (primarily reported as a complication of diverticulitis)
- May consider for patients meeting criteria above and who are not a candidates for Sarilumab Clinical Trial (Anschutz only)

**Dosing:** 400mg IV once (if < 50kg then 8mg/kg)
- Repeat dose x 1 after 12-24h may be considered
I. GENERAL INFORMATION

- Patients infected with the COVID-19 virus are potentially at increased risk of venous thromboembolism due to hospitalization, immobilization/isolation, and likely the infection itself.
- COVID-19 has been associated with a coagulopathic presentation that mimics DIC, which may be more prothrombotic than hemorrhagic.
- 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>
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</thead>
<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 70&lt;sup&gt;6&lt;/sup&gt; (If available)</td>
<td>TEG (MA) &gt; 70&lt;sup&gt;6&lt;/sup&gt; (If available)</td>
</tr>
<tr>
<td>Weight &lt;100 kg</td>
<td>Enoxaparin 40 mg QD</td>
<td>Enoxaparin 30 mg BID</td>
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<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>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU patients</th>
<th>D-dimer &lt;1500 AND</th>
<th>D-dimer 1500* OR</th>
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<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 70&lt;sup&gt;6&lt;/sup&gt; (If available)</td>
<td>TEG (MA) &gt; 70&lt;sup&gt;6&lt;/sup&gt; (If available)</td>
</tr>
<tr>
<td>Weight &lt;100 kg</td>
<td>Enoxaparin 40 mg QD</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 preliminary data from anti-Xa activity levels in UCH patients.

* This guideline does not endorse routinely performing Thromboelastography (TEG) in COVID-19 patients, particularly those on the floor, but use of the results, if ordered, may be considered. Available data from other populations indicate hypercoagulability is present in patients with TEG MA values > 70, although there are no outcomes data in COVID-19 to date. In addition, there are no clear data that incorporate other markers of inflammation, such as fibrinogen or ferritin, to drive anticoagulation choices. However, these markers have been notably elevated in severely ill 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 those with AKI may still have GFR > 30ml/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 drip and order a truncated, lower extremity DVT protocol (POCUS) as a confirmatory test.
   - 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).
   - 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:
   - For Enoxaparin: measure anti-Xa level 4 hours after 3rd dose. Goal = 0.3-0.5. Increase dose as guided by anti-Xa level. Consider using TEG.
   - When TEG monitoring available: Use Kaolin / heparinase

IV. GUIDANCE ON ANTICOAGULATION IS AVAILABLE THROUGH THE FOLLOWING ORGANIZATIONS:

- International Society of Thrombosis and Haemostasis
- American Society of Hematology
- Anticoagulation Forum
- American College of Cardiology
<table>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Study design</th>
<th>Eligible time to enrollment</th>
<th>Languages</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Risks</th>
<th>Benefits</th>
<th>Considerations</th>
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<tbody>
<tr>
<td>Hydroxychloroquine (ORCHID study, sponsored by PETAL network)</td>
<td>5 days HCQ vs placebo</td>
<td>Randomized double blind, placebo-controlled (1:1)</td>
<td>&lt; 48 h from admission, &lt; 10 d since positive test</td>
<td>English, Spanish, Arabic, Dutch, Italian, Vietnamese, Portuguese, French, Russian, German, Somali, Greek, Haitian Creole, Chinese (Mandarin/Traditional), Hebrew</td>
<td>One or more of the following symptoms: cough, fever (&gt;37.5 C / 99.5F), shortness of breath, sore throat</td>
<td>prisoner, pregnancy, breast feeding, seizure, porphyria CT, QTc &gt;500ms within 72h, diagnosis of long QT syndrome, following meds: amiodarone; cimétidine; dofétilide; phenobarbital; phenytoïn; sotalol; dose of HCQ in 10 days prior to enrollment, inability to receive enteral meds, inability to be contacted on d15, prior trial enrollment</td>
<td>QTc prolongation, elevation of LFT, rash, neurologic SE, cytopenias</td>
<td>Possible antiviral effect</td>
<td>People with prolonged QTc or other QTc prolonging medications could be at higher risk (see exclusion criteria). Consider whether to offer to those with elevated troponin</td>
</tr>
<tr>
<td>Remdesivir Severe arm (GS 5773)</td>
<td>Up to 10 days RDV</td>
<td>Open label</td>
<td>&lt; 4 d since first positive test</td>
<td>English, Spanish, Korean, Chinese, Vietnamese</td>
<td><strong>Hypoxia</strong> (&lt;94% on RA, or on supplemental oxygen) Pneumonia (on imaging)</td>
<td>participation in other clinical trial, concurrent treatment with other COVID-19 treatment &lt;24 prior to enrollment, multiorgan dysfunction, ventilated &gt;/=5 days, ALT or AST &gt;5x ULN, CrCl &lt;50, pregnant or breastfeeding</td>
<td>headache, bruising, infusion reaction, elevation of LFTs</td>
<td>possible antiviral effect</td>
<td>Excludes being on another study. May be available by EUA and if a patient qualifies, consider trial instead of EUA</td>
</tr>
<tr>
<td>Remdesivir Moderate arm (GS 5774)</td>
<td>Up to 10 days RDV</td>
<td>Open label</td>
<td>&lt; 4 d since first positive test</td>
<td>English, Spanish, Korean, Chinese, Vietnamese</td>
<td><strong>No Hypoxia</strong> (&gt;94% on RA at screening) Pneumonia (on imaging)</td>
<td>participation in other clinical trial, concurrent treatment with other COVID-19 treatment &lt;24 prior to enrollment, multiorgan dysfunction, ventilated &gt;/=5 days, ALT or AST &gt;5x ULN, CrCl &lt;50, pregnant or breastfeeding</td>
<td>headache, bruising, infusion reaction, elevation of LFTs</td>
<td>possible antiviral effect</td>
<td>Excludes being on another study. May be available by EUA and if a patient qualifies, consider trial instead of EUA</td>
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<tr>
<td>Study</td>
<td>Patient Selection</td>
<td>Endpoint Considerations</td>
<td>Other Considerations</td>
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<tr>
<td>Convalescent Plasma</td>
<td>1-2 units based on weight, Open label, No limit, English, Age &gt;=18, moderate disease (dyspnea, RR&gt;30, spO2&lt;93%), severe disease (moderate criteria + radiographic evidence of &gt;50% pulm involvement, supplementary O2 to maintain spO2 &gt;90%), or life-threatening disease (includes NIV, intubation, prone positioning to support O2, MOD)</td>
<td>Patient does not accept blood products.</td>
<td>Consider risk of transfusion. May exclude participation in other studies. Currently, no evaluation for neutralizing antibodies prior to administration.</td>
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<tr>
<td>Sarilumab</td>
<td>1 or more doses of 400mg vs placebo, Randomized double blind, placebo-controlled (2:1), &lt;14d test, Various (contact study team for details)</td>
<td>&gt;=18 yo, critical disease (use of HFNC, NIV, or intubation) without evidence of multiorgan dysfunction.</td>
<td>Active infection, treatment with anti-IL6 or JAKi in past 30 days, ANC &lt;2000, platelets &lt;50K, AST or ALT &lt;5x ULN, ECMO, possibility of untreated TB, participation in another double-blind clinical trial for COVID-19.</td>
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<tr>
<td>tPA</td>
<td>50mg vs 100mg vs SOC, Pragmatic, open label, randomized controlled, N/A, Hospital interpreters used to translate consent</td>
<td>Age 18-75, mechanically ventilated with ARDS (P/F &lt;150), neuro exam without focal or new deficits or MRI/CT within 4.5 hrs without e/o stroke</td>
<td>Active bleeding or high risk for bleeding, including CNS bleed (see study document for details); Cr &gt;3x baseline, ALT &gt;3x baseline, HD instability on norepi &gt;0.2, ECMO</td>
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Sponsor: Regeneron; PI Campbell

Risk of infection including UTI, pneumonia, cellulitis, diverticulitis and perforation. Risk of elevation of LFTs and cytopenia.

Patients concurrently enrolled in other COVID-19 therapeutic trials are eligible, as long as the other trials allow co-enrollment as well.
Hydroxychloroquine
ORCHID Trial (run by PETAL Network, sponsored by NHBLI)

**Rationale/Mechanism:** Low endosomal pH plays a role in allowing viral replication inside the target cell. Endosomal acidification inhibitors such as Chloroquine and Hydroxychloroquine, may have a potential role in treatment.

**Trial design:** randomized, double-blind, placebo-controlled phase 3 trial. 1:1 randomization to hydroxychloroquine or placebo (50% chance of receiving the study drug)

**Inclusion criteria:**
- Hospitalized adults 18+ years of age with confirmed SARS-CoV-2 PCR positive within last 10 days
- One or more the following symptoms: cough, fever (>37.5 C / 99.5F), shortness of breath, sore throat

**Exclusion criteria:**
- Pregnancy or breastfeeding
- Prisoner
- >10 days since symptom onset
- >48 hours since hospital arrival
- last ECG (within 72 hours) with QTc > 500ms
- Known diagnosis of long QT syndrome
- Seizure disorder
- Porphyria cutanea tarda
- Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol
- Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment
- Inability to receive enteral medications

**Dosing:** Hydroxychloroquine 400mg twice daily for 2 doses, then 200mg twice daily for 8 doses (5 days)

**Monitoring:** ECG or telemetry to follow up on QTc 24 to 48 hours after study drug initiation

**Adverse reactions:** QTc prolongation

<table>
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<tr>
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</tbody>
</table>
**Rationale/Mechanism:** Nucleotide analogue with activity against coronaviruses (SARS, MERS, SARS2) in vitro and in animal studies.

**Trial design:** Open-label, single arm, non-randomized trial. All patients receive the study drug (intravenous infusion) for up to 10 days. Treatment will stop if patient is discharged earlier than the completion of assigned therapy duration.

**Inclusion criteria:**
- Hospitalized adults 18+ years of age with confirmed COVID-19 with PCR/NAAT (within 4 days of first/initial ever positive PCR result from Randomization)
- Radiographic evidence of pneumonia
- Oxygen saturation ≤94% on room air or requiring oxygen supplementation

**Exclusion criteria:**
- Participation in any clinical trial involving treatment of COVID-19
- Receipt of any pharmacologic therapy (with known or possible direct antiviral activity) for COVID-19 for up to 24 hours prior to study drug dosing. Anti-inflammatory therapy is allowed.
- Multi-organ failure
- On ECMO for 5 or more days
- AST/ALT >5x ULN
- Creatinine clearance <50ml/min using Cockcroft-Gault formula
- Pregnant or breastfeeding

**Dosing:** 200mg IV day 1, and 100mg IV daily up to 10 days (study treatment stopped if patient gets discharged earlier)

**Adverse reactions:** Nausea, vomiting, transaminase elevation

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**Remdesivir GS-5774 - MODERATE arm – STUDY CLOSED**

Sponsored by Gilead

**Rationale/Mechanism:** Nucleotide analogue with activity against coronaviruses (SARS, MERS, SARS2) in vitro and in animal studies.

**Trial design:** Open-label, three arm, randomized trial. Patients randomized to 5-day or 10-day course. Treatment will stop if patient is discharged earlier than the completion of assigned therapy duration.

**Inclusion criteria:**
- Hospitalized adults 18+ years of age with confirmed COVID-19 with PCR/NAAT (within 4 days of first ever positive PCR result from randomization)
- Oxygen saturation >94% on room air at screening
- Radiographic evidence of pulmonary infiltrates

**Exclusion criteria:**
- Participation in any clinical trial involving treatment of COVID-19
- Receipt of any pharmacologic therapy (with known or possible direct antiviral activity) for COVID-19 for up to 24 hours prior to study drug dosing. Anti-inflammatory therapy is allowed.
- Mechanical ventilation at screening
- AST or ALT >5x ULN
- Creatinine clearance <50ml/min using Cockcroft-Gault formula
- Pregnant or breastfeeding

**Dosing:** 200mg IV day 1, and 100mg IV daily up to 5 or 10 days, whichever assigned. Treatment will stop if any elevations in ALT > 5x ULN; or ALT > 3x ULN and total bilirubin > 2x ULN, confirmed by immediate repeat testing, OR CrCl< 30 mL/min, OR any severe AE or ≥ grade 3 AE suspected to be related to remdesivir.

**Adverse reactions:** Nausea, vomiting, transaminase elevation.

### Contacts

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Rationale/mechanism: Some COVID-19 patients have been found to have significant immune activation and cytokine release leading to end-organ injury. Sarilumab is a monoclonal antibody directed against membrane-bound and soluble IL-6 receptors. IL-6 receptor blockade may moderate the end-organ effects of immune activation.

Trial design and treatment protocol: Adaptive Phase 2/3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19. Participants randomized 2:1 to sarilumab 400 mg IV or placebo (33.3% probability of receiving placebo). Patient will receive repeat doses at 24 hours after the initial administration if the patient meets one of the following criteria: remains febrile, fails to improve gas exchange (as measured by ventilator settings or O2 requirements), is hemodynamically unstable, or exhibits objective evidence of clinical worsening. Patient may also receive repeat weekly doses if they continue to require any supplemental oxygen above baseline.

Inclusion criteria:
- Hospitalized adult patients (18+ years of age) with laboratory confirmed COVID-19 by PCR/NAAT (up to 14 days prior to enrollment from first positive result)
- Evidence of pneumonia by chest radiograph, chest CT, or auscultation (rales, crackles)
- Requiring oxygenation supplementation (NIPPV, HFNC, mechanical ventilation)

Exclusion criteria:
- Not expected to survive >48 hours (as assessed by investigator)
- Labs: ANC <2000, ALT/AST >5x ULN, and platelet count <50,000
- Multiorgan failure: AKI on HD or CRRT, multiple pressors, LFTs as above
- Treatment with IL-6 inhibitor or Janus kinase inhibitor (JAKi) in the past 30 days
- Current simultaneous treatment with leflunomide and methotrexate
- Active TB, history of incompletely treated TB, or suspected or known extrapulmonary TB
- Active or suspected bacterial or fungal infection
- Participation in a double-blind clinical trial (participation in an open-label study of any other COVID-19 treatment is permitted)

Adverse reactions: Neutropenia, transaminitis, hypersensitivity reaction, hypercholesterolemia, colitis.

Notes: Sarilumab is not dialyzable, so patients can continue HD or CRRT.

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Convalescent Plasma
(PI: David Beckham, Lakshmi Chauhan)

Study design: Prospective, open-label observational cohort study.

Inclusion Criteria:
- Age ≥ 18 years
- Laboratory confirmed diagnosis of infection with SARS-CoV-2
- Admitted to an acute care facility for the treatment of COVID-19 complications
- Moderate to severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease
- Informed consent provided by the patient or healthcare proxy

Moderate COVID-19 is defined by one or more of the following:
- Dyspnea
- Respiratory frequency >30/min
- Blood oxygen saturation <93%

Severe COVID-19 is defined by one or more of the following:
- Moderate criteria plus one of the following:
  - Radiologic evidence of >50% pulmonary involvement
  - Requirement for supplementary oxygen therapy to maintain blood oxygen saturation >90%

Life-threatening COVID-19 is defined as one or more of the following:
- Respiratory failure requiring mechanical ventilation or non-invasive non-rebreather oxygen support
- Prone positioning to support oxygenation
- Multiple organ dysfunction or failure

Scoring system for allocation of plasma:

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>PaO2/FiO2</td>
<td>&gt;400 mmHg</td>
<td>200-400 mmHg or O2 &gt; 5L/min</td>
<td>100-200 mmHg or mechanical ventilation</td>
<td>Prone ventilation, ECMO</td>
</tr>
<tr>
<td>Cardiovascular (Hypotension)</td>
<td>MAP &gt; 70 mmHg</td>
<td>MAP &lt; or = 70mmHg</td>
<td>On norepi &lt; or= 1 mcg/kg/min</td>
<td>Norepi &gt; 0.1 mcg/kg/min or more than 1 pressor</td>
</tr>
<tr>
<td>Renal (S. Creat)</td>
<td>&lt;1.2</td>
<td>1.2-2.0</td>
<td>2.0-4.0</td>
<td>&gt; 4.0 or on dialysis</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;75</td>
<td>60-75</td>
<td>40-60</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Days since admission</td>
<td>&gt;7</td>
<td>5-7</td>
<td>3-5</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>Pregnancy status</td>
<td>No or N/A</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Immunocompromised state-immunosuppressive medications, transplant recipient</td>
<td>No</td>
<td>Immuno-suppressive medications including chemotherapy</td>
<td></td>
<td>Functioning organ transplant</td>
</tr>
</tbody>
</table>

Priority for convalescent plasma will be given to patient with highest score
Process for allocation and administration of convalescent plasma:

1. Inpatient ID team to be consulted to decide if patient is an appropriate candidate for allocation of convalescent plasma.
2. ID Team can call or send Epic secure chat message to Lakshmi Chauhan or David Beckham to help with consent and orders for convalescent plasma between 8am-3pm daily, including weekends.
3. Patients will be enrolled under the FDA expanded access protocol and will also be included in a multi-institutional prospective cohort study.
4. Transfusion of 1 or 2 units per patient to be allocated based on weight. Only one dose permitted (no re-dosing).
5. There is limited capacity to consent and prepare convalescent plasma per day, so attached scoring system will be used as a guide to refer patients. Higher score may indicate patients with more severe disease or patients at higher risk for progression to severe disease, and therefore those who may benefit most.
6. Neutralizing antibody titer is not being assessed in donor plasma at this time. ABO matched plasma is given whenever possible.
7. Pre-medication can be administered by primary team if needed.
8. Note that enrollment in convalescent plasma trial may exclude patients from other clinical trials (for example, remdesivir trials; please consult with your local clinical trials coordinator). Patients would be eligible for sarilumab trial.

Forms to be signed for each eIND transfusion:

1. Transfusion consent
2. Additional COVID-19 transfusion consent
3. CCP eIND consent.

Please contact Lakshmi Chauhan if you believe your patient is good candidate for convalescent plasma.
Fibrinolytic Therapy to Treat ARDS in COVID-19  
(PI: Ernest Moore, MD)

**Rationale:** ARDS in COVID-19 is associated with fibrin-platelet microthrombi. Administration of tissue plasminogen activator (tPA) in patients with severe ARDS may improve pulmonary gas exchange and oxygenation via a decrease in pulmonary vascular microthrombi.

**Study design:** Pragmatic, adaptive, open label, randomized controlled trial. Sequential enrollment tPA 50mg vs control (standard of care), tPA 100mg vs control, then tPA 50mg vs tPA 100mg. Re-bolusing of tPA, at the same dose, is permitted in the intervention groups in those patients who show an initial transient response (>20% improvement of PaO2/FiO2 over pre-infusion of alteplase, that is not sustained up to 24 hours after randomization); the repeat dose will be given only 24 hours after the initial tPA administration.

**Inclusion criteria:**
- Age 18-75
- Mechanically ventilated with ARDS (P/F <150)
- Neuro exam without focal or new deficits, or MRI/CT within 4.5 hrs without evidence of stroke

**Exclusion criteria:**
- Active bleeding
- Acute myocardial infarction or history of myocardial infarction within the past 3 weeks or cardiac arrest during hospitalization
- Hemodynamic instability with Noradrenaline >0.2mcg/Kg/min
- Acute renal failure (escalating renal failure with creatinine >3 times baseline)
- Liver failure (escalating liver failure with ALT > 3 times baseline)
- Cardiac tamponade
- Bacterial endocarditis
- Severe uncontrolled hypertension defined as SBP>185mmHg or DBP>110mmHg
- CVA (stroke), history of severe head injury within prior 3 months, or prior history of intracranial hemorrhage
- Seizure during pre-hospital course or during hospitalization for COVID-19
- Diagnosis of brain tumor, arterio-venous malformation (AVM) or ruptured aneurysm
- Currently on ECMO
- Major surgery or major trauma within the past 2 weeks
- GI or GU bleed within the past 3 weeks
- Known bleeding disorder
- Arterial puncture at a non-compressible site within the past 7 days
- Lumbar puncture within past 7 days
- Pregnancy
- INR > 1.7 (with or without concurrent use of warfarin)
- Platelet count < 100 x 10^9/L or history of HITT
- Fibrinogen < 300mg/dL
- Known abdominal or thoracic aneurysm
- History of CNS malignancy or CNS metastasis within past 5 years
- History of non-CNS malignancy within the past 5 years that commonly metastasizes to the brain (lung, breast, melanoma)
- Prisoner status

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