COVID-19 Treatment Recommendations, by disease severity

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Panel's Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Hospitalized or Hospitalized but Does Not Require Supplemental Oxygen</td>
<td>No specific antiviral or immunomodulatory therapy recommended. The Panel recommends against the use of dexamethasone (AI)</td>
</tr>
</tbody>
</table>
| Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO) | Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first (AI)\textsuperscript{c,d}  
or  
Remdesivir (dose and duration as above) plus dexamethasone\textsuperscript{e}  
6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first (BIII)  
If remdesivir cannot be used, dexamethasone\textsuperscript{e} may be used instead (BIII) |
| Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation | Dexamethasone\textsuperscript{e}  
6 mg IV or PO daily for up to 10 days or until hospital discharge whichever comes first (AI)  
or  
Remdesivir (dose and duration above) may be added to dexamethasone, though limited evidence suggests benefit (AII) |
| Hospitalized and Requires Invasive Mechanical Ventilation or ECMO | Dexamethasone\textsuperscript{e} at the dose and duration discussed above (AI)  
**Remdesivir use among hospitalized patients requiring invasive mechanical ventilation or ECMO did not improve mortality or recovery time, and its use in this population is not recommended.** |

Source: NIH COVID-19 Treatment Guidelines, Oct 9, 2020
COVID-19 Therapies at UCHealth: Criteria for use and additional information

A. Remdesivir (Veklury®). Based on the available data, remdesivir received FDA approval on October 22, 2020 for the treatment of adults and children ages 12 years and older weighing ≥ 40 kg with confirmed COVID-19 requiring hospitalization. Criteria for use at UCHealth and other considerations are below, based on the currently available data and drug supply. Note that criteria are subject to change based on new data and supply/demand.

i. UCHealth criteria for use:
   - Confirmed COVID-19 positive by SARS-CoV-2 PCR
   - Symptom duration ≤ 14 days (longer symptom duration considered if transplant recipient or other severely immunocompromised host)
   - Hypoxia requiring supplemental O2 but not high-flow, NIV, MV, or ECMO
      - Patients requiring high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and/or ECMO at baseline are unlikely to benefit from remdesivir based on review of published evidence; use of remdesivir in these circumstances should weigh risk vs. benefit, including consideration of drug cost and unproven efficacy in these populations.
      - Remdesivir may be continued if patients progress to mechanical ventilation or ECMO.
   - ALT < 5x ULN
   - CrCl ≥ 30 mL/min, or receiving CRRT. Remdesivir may be continued if CrCl falls below 30mL/min or CRRT is discontinued.
      - The active form of remdesivir is highly intracellularly concentrated and renal impairment does not appear to substantially impact its clearance. The amount of cyclodextrin present is much less than that compared to IV voriconazole, and duration of use is short. Given a short duration of treatment, the risk is likely minimal and may be outweighed by the potential benefit, therefore it may be reasonable to continue use for those who start remdesivir and CrCl declines to <30 mL/min.

ii. Dose: 200mg IV on day 1, 100mg IV on days 2-5

iii. Duration of treatment: Up to 5 days, or until hospital discharge, whichever occurs first.

iv. Notes:
   - Hepatic function tests should be monitored daily while on remdesivir.
   - All adverse drug reactions (including death) should be reported via RL Solutions.
   - At UCHealth AMC, remdesivir is a tier 2 protected antimicrobial (i.e., order can be approved by verifying pharmacist if criteria above are met. Order requires approval from ID Pharmacy / Antimicrobial Stewardship if requested outside of the above criteria (send secure chat to “AMC Stewardship”).

B. Dexamethasone. Dexamethasone is indicated in patients who require supplemental oxygen, including mechanical ventilation or ECMO. It is NOT recommended for patients who do not require supplemental O2.

i. Dose: 6mg IV or PO per day

ii. Alternative glucocorticoids can be considered if dexamethasone is unavailable:
   - Prednisone 40mg per day
   - Methylprednisolone 32mg per day (once daily or 2 divided doses)
   - Hydrocortisone 160mg per day (2-4 divided doses)

iii. Duration: up to 10 days, or until hospital discharge, whichever occurs first.

iv. Notes:
   - Weigh risk of steroid use or continuation in the overall clinical context, including concurrent active or latent infections, other immunosuppression, hyperglycemia, etc.
   - Recommend consultation with OB/GYN regarding the use of steroids in pregnancy.

C. Other off-label and non-approved therapies are generally not recommended outside of a clinical trial, including: COVID-19 convalescent plasma (CCP). There are currently insufficient data to recommend for or against the use of CCP. Clinical judgment should be exercised for patients who might benefit, in which case CCP can be accessed by clinical trial enrollment (PassItOn study), or by emergency use authorization (EUA). If giving CCP under EUA, provider must read the “FDA Fact Sheet For Providers,” provide the patient / caregiver with the “FDA Fact Sheet For Patients and Caregivers,” discuss risks and alternatives, and obtain verbal consent.
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>Evidence</th>
<th>Comments/Recommendation</th>
</tr>
</thead>
</table>
| Remdesivir           | Nucleoside analog: inhibits viral RNA polymerase | *In Vitro*—low EC<sub>50</sub> value = 0.77 μM  
**Lancet RCT vs. Placebo; ACTT-1 Results; Gilead brief** | FDA Approved Oct 22nd for use in hospitalized patients with COVID-19. Most studies show benefit in patients requiring low O2. Lack of benefit observed in critical COVID-19 (i.e. mechanically ventilated or require high intensity O2). Recent in vitro results demonstrate potential antagonism with concurrent hydroxychloroquine. |
| Corticosteroids      | Anti-inflammatory              | RECOVERY Trial – RCT of Dexamethasone 6mg q24h x 10 days vs. supportive care alone  
**Recovery trial site: Medrxiv preprint** | **Based on substantial mortality benefit, use of dexamethasone 6mg daily (or equivalent dose of prednisone/methylprednisone) should be considered if contraindications absent and patient on supplemental oxygen or mechanically ventilated** |
Joyner, et al. 2020 – Preprint, n = 35,322, showing trends toward benefit in those receiving within 3 days of diagnosis, and receiving high-titer plasma  
**FDA approved EUA use.** |
| Baricitinib          | Janus kinase (Jak) inhibitor   | Lilly press release – Unpublished ACTT-2 data suggest that baricitinib use with remdesivir led to a one day reduction in time to recovery compared to remdesivir alone. | 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. |
| LY-CoV555 (Bamlanivimab) | Monoclonal antibody directed against receptor binding domain of SARS-CoV-2 S protein. | Chen, et al. 2020 – Interim Analysis of Phase 2 RCT, demonstrating 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).  
**Request for EUA has been submitted. No availability at this time.** |
| REGN-COV2 (REGN10933 + REGN10987) | Fully human, IgG1 monoclonal antibody that binds the receptor binding domain of the SARS-CoV-2 S protein. | 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 (including being over 50 years of age; body mass index greater than 30; cardiovascular, metabolic, lung, liver or kidney disease; or immunocompromised status) (combined dose groups; nominal p = 0.0065)  
**Request for EUA has been submitted. No availability at this time.** |
| ACE-I / ARB          | Anti-hypertensives             | Theoretical increased viral entry through animal models showing RAAS inhibition leads to ACE-2 upregulation.  
**No evidence to date of a strong association.**  
Kassiri et al. ACE2 knockout mice have adverse ventricular remodeling  
Oudit et al. ACE-2 downregulation associated with myocardial dysfunction during SARS-CoV-1  
Zhang P, et al. Retrospective analysis of ACEi/ARB use | 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.  
Insufficient evidence to avoid/discontinue ACE-I or ARBs when compelling indications for their use exists.  
Insufficient evidence to recommend use of these agents for treatment of COVID-19. |
<p>| <strong>NSAIDs</strong> | Anit-inflammatory, analgesic, anti-pyretic | <strong>Uncontrolled case report of 4 patients</strong> 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/analgies in COVID-19 patients. | <strong>EMA, FDA and WHO</strong> 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. <strong>Recent evidence</strong> not supportive of initial concern with worse COVID-19 related outcomes in patients using NSAID vs. APAP |
| <strong>Ruxolitinib, acalabrutinib, other TKIs</strong> | Janus kinase (Jak) inhibitor AAK1 inhibition impacting viral entry and anti-inflammatory | <strong>Theoretical</strong>, no published clinical evidence available presently. <strong>Ruxolitinib</strong> pilot RCT results <strong>Acalabrutinib</strong> 19 patient observational report | Insufficient evidence to recommend use presently outside of clinical trial. |
| <strong>IVIG</strong> | Neutralizing antibodies, immunomodulating effects | <strong>Cao et al. case report, n=3</strong> | Presence of neutralizing antibodies not expected, theoretical immunomodulating effects. <strong>SCCM guidelines</strong> recommend against use. |
| <strong>Interferon</strong> | Direct viral effects and indirect stimulation of innate immune responses against viral infection | Mostly reports of <strong>combination use</strong> 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 | No direct comparison studies in SARS-CoV-2. <strong>SCCM guidelines</strong> do not recommend. |
| <strong>Statins</strong> | Pleiotropic, immunomodulating effects, cardioprotective | No published evidence, based on mechanism and extrapolation from other data | Not routinely recommended, consider adding/continuing if other compelling indication exists for statin. |
| <strong>Favipiravir</strong> | RNA polymerase inhibitor | <strong>In Vitro</strong> EC50 higher then remdesivir and CLQ/HCLQ. <strong>Cai et al. 2020</strong>—open label, prospective comparison vs. LPV/r | Favipiravir is under investigation, but is not approved for use in the U.S., and no active study sites listed in U.S. |
| <strong>Zinc</strong> | Unclear, inhibits viral replication | No published studies, theoretical | <strong>Recommend against routine use</strong> |
| <strong>Vitamin C</strong> | Unclear, likely immunomodulating | No published evidence, ongoing high-dose IV study in China | Low quality evidence, recommend against routine use |
| <strong>Colchicine</strong> | Anti-inflammatory, reduces the production of active IL-1β | <strong>Deftereos et al.</strong> Open-label, randomized clinical trial, n = 105, 55 colchicine, 50 control | Pilot study showed potential benefit of colchicine. Not currently recommended outside the context of a clinical trial. |
| <strong>Tocilizumab and other IL-6 antagonists</strong> | <strong>IL-6 receptor antagonist</strong> Theoretical management of patients with hyperinflammatory response (aka cytokine release) | <strong>Case series</strong> (n=20), described rapid improvement in patients from oxygenation and inflammatory markers after 400mg dose. Only 2 patients were intubated at time. <strong>Price et al.</strong>—Retrospective observational cohort of 152 tocilizumab patients, showed similar survival despite higher inflammatory markers than controls. <strong>Gualardi et al.</strong>—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 three times higher. The Regeneron sponsored trial has been terminated due to lack of efficacy and evidence of potential harm. | <strong>Low quality evidence, with high risk of bias, suggests tocilizumab is associated with improvements in inflammatory markers and mortality. Concerns with safety, particularly with new or worsening infections (TB, fungal, other bacterial) due to immunosuppressive characteristics.</strong> Higher quality clinical trials for IL-6 inhibitors (which we do not have full data for) including the Roche sponsored and Regeneron sponsored studies have been halted as there was no reduction of death, severe symptoms, or ICU admission observed. <strong>Given the lack of evidence of efficacy, issues with safety, in addition to benefit of other agents such as dexamethasone, tocilizumab or other IL-6 inhibitors should not be given outside of a clinical trial.</strong> |
| <strong>Hydroxychloroquine (HCLQ)/Chloroquine (CLQ)</strong> | Anti-inflammatory and inhibition of viral entry | <strong>In Vitro</strong>—HCLQ EC50 = 0.72 μM &amp; CLQ EC50 = 5.47 μM Clinical: <strong>NIH halts trials for hydroxychloroquine</strong>. Many clinical trials with hydroxychloroquine have terminated at request of DSMBs for lack of efficacy observed in analysis of these trials. | <strong>Multiple negative studies among hospitalized patients and those for secondary prophylaxis, Hydroxychloroquine is not recommended for use.</strong> |
| <strong>HIV Protease Inhibitors:</strong> | Inhibition of viral protease | <strong>LPV/r</strong>: in vitro extrapolated from SARS-CoV-1 and MERS-CoV. - <em>Chu-2004</em> and <em>Chan-2003</em> retrospective SARS-CoV-1 - <em>NEJM</em> prospective study of LPV/r vs. supportive care - * driv L—Janssen* found no relevant in vitro activity <strong>ATV</strong>: no in vitro studies, but reports that models show high affinity for docking | <strong>SOLIDARITY</strong> showed no benefit of LPV/r in severe and critical COVID-19. NEJM 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. |</p>
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mechanism</th>
<th>In vitro EC_{50}</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribavirin (RBV)</td>
<td>Nucleoside analog: inhibits viral RNA polymerase</td>
<td>109.5 μM</td>
<td>No clinical evidence for SARS-CoV-2, some combination with LPV/r or IFN evidence from SARS-CoV-1. 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>2.12 μM</td>
<td>Evidence in flu with shorter symptom length 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>

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.

*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.*
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>
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<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 70k</td>
<td>TEG (MA) &gt; 70k</td>
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<tr>
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<td>(Only if available, see info below)</td>
<td>(Only if available, see info below)</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>
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</thead>
<tbody>
<tr>
<td></td>
<td>TEG (MA) ≤ 0k</td>
<td>TEG (MA) &gt; 0k</td>
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* 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
   d. American College of Cardiology
### UCH Anschutz Ongoing Clinical Trials for COVID-19 (Inpatient)

<table>
<thead>
<tr>
<th></th>
<th>I-SPY +RDV in all pts</th>
<th>Convalescent plasma PassItOn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max latency from PCR+ to enrollment (days)</td>
<td>No limit</td>
<td>14 days (from symptom onset or PCR diagnosis)</td>
</tr>
<tr>
<td>Study drug to placebo ratio - %</td>
<td>No placebo, open-label rx only (4 arms)</td>
<td>1:1 (50%)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>high flow oxygen (≥6L by nasal cannula or mask delivery system) OR intubated for &lt;72 hours Confirmation of SARS-CoV-2 infection by PCR</td>
<td>Currently hospitalized or in the ED with anticipated admit. (O2 not required) 1+ of the following symptoms: Cough, fevers/chills, shortness of breath</td>
</tr>
<tr>
<td>Exclusion criteria (the list is not comprehensive)</td>
<td>Pregnant/ breastfeeding Allergies to study medication (or their components) Acute or chronic liver disease with Child-Pugh&gt;11 SNF resident&gt;6 mo Estimated mortality &gt;50% in next 6 mo due to comorbidity(ies)</td>
<td>Pooled Ig in the past 30 days Contraindications to transfusion or hx of reaction to blood products Planned discharge &lt;24 hours from enrollment Enrollment in another passive immunity trial</td>
</tr>
<tr>
<td>Anti-viral allowed?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Anti-inflammatory allowed?</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Participation in another clinical trial</td>
<td>✗</td>
<td></td>
</tr>
<tr>
<td>Contacts</td>
<td>Jeffrey McKeehan, Ellen Burnham, Marc Moss</td>
<td>Shelby Shelton, Jennifer Peers, Lakshmi Chauhan, Adit Ginde, Kevin Sullivan,</td>
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- Anti-viral allowed? Yes
- Anti-inflammatory allowed? Yes
- Participation in another clinical trial No

Contacts: Jeffrey McKeehan, Ellen Burnham, Marc Moss

Shelby Shelton, Jennifer Peers, Lakshmi Chauhan, Adit Ginde, Kevin Sullivan,
I-SPY

The I-SPY COVID-19 study is a multi-center, Phase 2, open-label platform trial designed to rapidly test novel therapies for critically ill patients with severe or immediately life threatening COVID-19, with the goal of reducing mortality and morbidity, as well as the impact on healthcare utilization.

If interested in the therapeutic portion of the trial, participants will be randomized to control or treatment therapy, with both groups receiving standard of care backbone interventions including supportive care for Acute Respiratory Distress Syndrome (ARDS), including daily EUA remdesivir (x5 or x10 days) and if needed, lung protective ventilation. Steroid therapy is allowed/encouraged. Participants will be asked to sign a consent form for the backbone treatment and a SINGLE specific investigational agent arm to which they are assigned. Up to four investigational medications may be active at any given time.

The current four agents to be tested include:

- **Apremilast**: (Otezla®) inhibits PDE4 intracellularly and has anti-inflammatory properties
- **Cenicriviroc**: a dual-CCR2/CCR5 antagonist, has potent anti-inflammatory and anti-fibrotic activity
- **Icatibant**: (Firazyr) specific antagonist of bradykinin B2 receptors
- **Razuprotafib**: designed to attach to and block vascular endothelial protein tyrosine phosphatase (VE-PTP), a key negative regulator of Tie2. Reduced Tie2 activity is known to cause vascular instability in various diseases.

Agents can seamlessly be added or dropped from the trial without interruption to the trial, based on safety and effectiveness. Agents will be approved by IRBs and be in the queue for addition once other agents leave. *All investigational medications and EUA remdesivir will be provided by the study sponsor.*

Additionally, an observational cohort of patients with similar clinical stages of COVID-19 will be followed via medical records. The goal of this registry cohort is to better understand how patients enrolled in the clinical trial compare to other local patients. In addition, data will be shared with the local clinical team.

Participants will continue on the study until protocol completion or removal. Regimens will be dropped if they are not sufficiently effective. The **primary endpoint** is time to achieve a durable COVID-19 status level 4 or lower. For this trial, a durable level is defined as at least 48 hours at COVID level 4 or less (nasal prongs oxygen) without returning to high flow oxygen or intubation. 1000 participants will be enrolled across all sites, with up to 50 participants enrolled at the University of Colorado Hospital.

**Inclusion Criteria.** Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Male or Female, at least 18 years old
2. Admitted and placed on high flow oxygen (greater than 6L by nasal cannula or mask delivery system) or intubated for the treatment of (established or presumed) COVID-19.
3. Informed consent provided by the patient or health care proxy.
4. Confirmation of SARS-CoV-2 infection by PCR prior to randomization.
Exclusion Criteria

1. Pregnant or breastfeeding women
2. History of allergic reactions attributed to compounds of similar chemical or biologic composition to Study Agent based on review of the medical record and patient history.
3. Comfort measures only.
4. Acute or chronic liver disease with a Child-Pugh score greater than 11.
5. Resident for more than six months at a skilled nursing facility.
6. Estimated mortality greater than 50% over the next six months from underlying chronic conditions.
7. Time since requirement for high flow oxygen or ventilation no greater than 72 hours.
8. Anticipated transfer to another hospital which is not a study site within 72 hours.

<table>
<thead>
<tr>
<th>Contacts</th>
<th>Division</th>
<th>E-Mail</th>
<th>Phone</th>
</tr>
</thead>
<tbody>
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</tr>
</tbody>
</table>
**Convalescent Plasma – PassItOn**

PassItOn is an NIH-sponsored, multi-site, investigator-initiated, blinded, placebo-controlled, randomized clinical trial evaluating convalescent donor plasma for the treatment of adults hospitalized with COVID-19. Plasma will be collected and distributed to sites through Vanderbilt University Medical Center’s blood donation center partner. Anti-SARS-CoV-2 antibody quantification assays will be completed on donor plasma at Vanderbilt University Medical Center (VUMC) prior to plasma distribution. Only plasma with antibody quantification above the neutralizing threshold will be used in the trial.

Participants will be randomized 1:1 to convalescent plasma versus placebo. Randomization will be completed in permuted blocks and stratified by site, sex, and age. Transfusion of convalescent plasma or placebo will be administered as a single dose by clinical or research personnel while the patient is hospitalized and within 24 hours of randomization. Participants randomized to active treatment will receive 1 unit of convalescent plasma, while patients randomized to placebo will receive 250 ml of lactated Ringer’s with multivitamins.

Clinical outcomes will be measured using the COVID-19 7-point Ordinal Clinical Progression Outcomes Scale at Day 15, among adults hospitalized with COVID-19. Assessment on days 1-7 (or less if discharged before day 7), day 8, day 15, and day 29. All other treatment decisions will be made by treating clinicians without influence from the protocol. Administration of other antiviral medications and immunomodulating medications, including corticosteroids, will be made by treating clinicians and will be recorded in the case report form.

**Inclusion Criteria**
1. Age greater than or equal to 18 years of age
2. Currently hospitalized or in an emergency department with anticipated hospitalization.
3. Symptoms of acute respiratory infection, defined as one or more of the following:
   a. Cough
   b. Chills, or a fever (greater than 37.5° C or 99.5° F)
   c. Shortness of breath, operationalized as a patient having any of the following:
      i. Subjective shortness of breath reported by a patient or surrogate.
      ii. Tachypnea with respiratory rate greater than 22 breaths per minute.
      iii. Hypoxemia, defined as SpO2 less than 92% on room air, new receipt of supplemental oxygen to maintain SpO2 greater than or equal to 92%, or increased supplemental oxygen to maintain SpO2 greater than or equal to 92% for a patient on chronic oxygen therapy
4. Laboratory-confirmed SARS-CoV-2 infection within the past 14 days

**Exclusion Criteria**
1. Prisoner
2. Unable to randomize within 14 days after onset of acute respiratory infection symptoms
3. Patient, legal representative, or physician not committed to full support (Exception: a patient who will receive all supportive care except for attempts at resuscitation from cardiac arrest will not be excluded.)
4. Inability to be contacted on Day 29-36 for clinical outcome assessment
5. Receipt of pooled immunoglobulin in the past 30 days
6. Contraindications to transfusion or history of prior reactions to transfused blood products
7. Plan for hospital discharge within 24 hours of enrollment
8. Previous enrollment in this trial
9. Enrollment in another clinical trial evaluating monoclonal antibodies, convalescent plasma, or another passive immunity therapy

**Contact information**

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