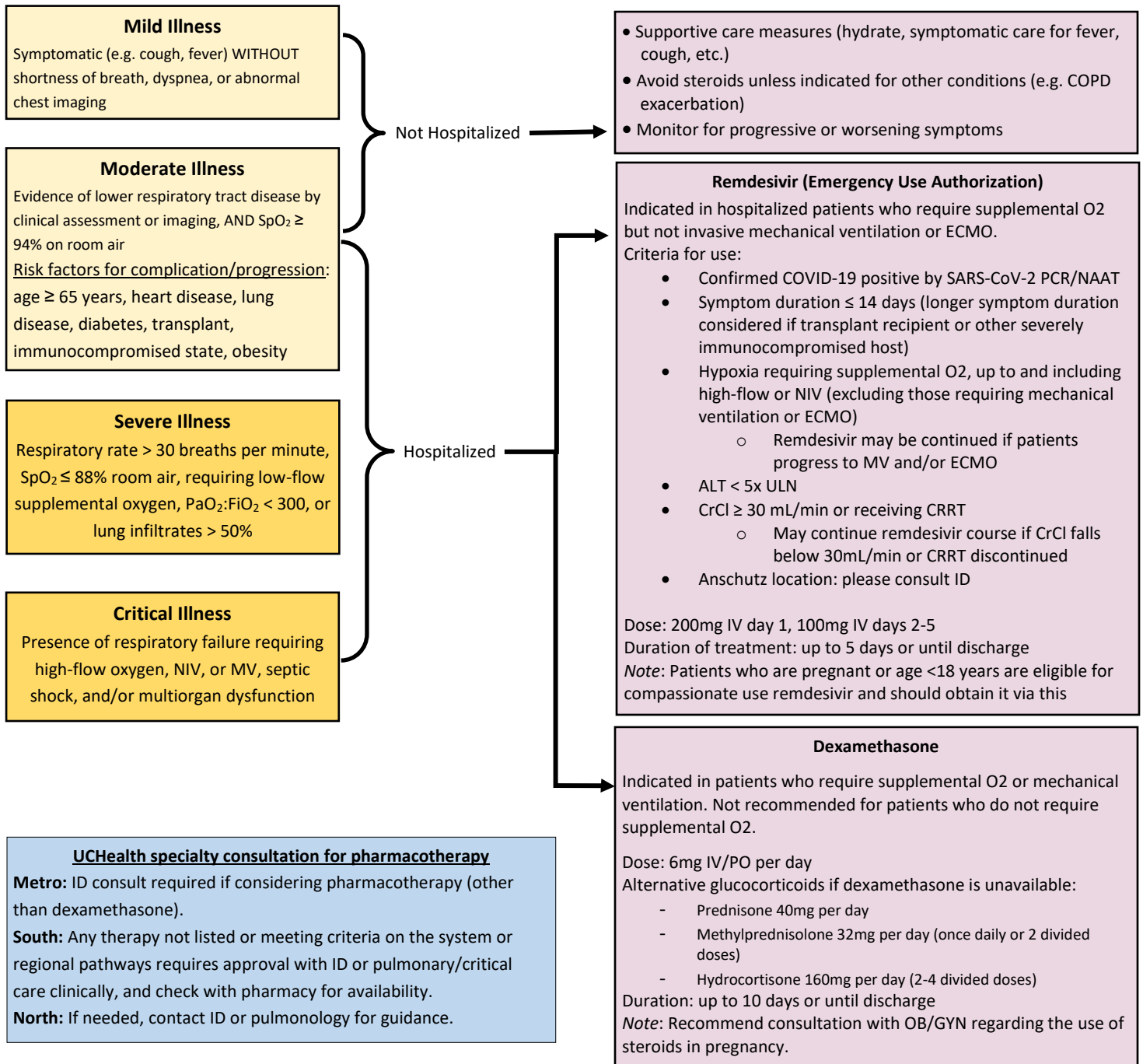


# UCHealth COVID-19 Pharmacotherapy Guidance (last updated 8.25.20)

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

### General Considerations:

- Optimize supportive care based on clinical status
- VTE Prophylaxis (see UCH COVID-19 Anticoagulation Recommendations on following pages)
- 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 process (negative cultures, low procalcitonin < 0.5, etc.)
- Additional pharmacotherapy management considerations based on clinical status



Please view these links for national society guidelines on COVID-19 therapeutics:

1. [Infectious Diseases Society of America – updated 6/22/20](#)
2. [National Institute of Health](#)
3. [Society of Critical Care Medicine](#)

**Other off-label therapies are not recommended outside of a clinical trial.** See attached pages for evidence summary of proposed agents and summary of ongoing clinical trials at Anschutz.

## COVID-19 Therapies at UCHealth

### 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 based on new data and supply/demand.

- **Criteria for use:**
  - Confirmed COVID-19 positive by SARS-CoV-2 PCR/NAAT
  - Duration of symptoms  $\leq$  14 days (longer symptom duration allowed if transplant recipient or other severely immunocompromised host)
  - Hypoxia requiring supplemental oxygen (excluding those requiring invasive mechanical ventilation or extracorporeal membrane oxygenation at time of remdesivir consideration/prescribing; however, remdesivir may be continued for those who initiate remdesivir on low/high-flow/NIV and progress to MV and/or ECMO)
  - ALT  $<$  5x ULN
  - CrCl  $\geq$  30 mL/min or receiving CRRT (SBECD present in remdesivir is expected to be adequately removed by CRRT)
  - ID consultation required at AMC location
- **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 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.
  - Remdesivir use for CrCl  $<$  30mL/min is risk:benefit due to unclear remdesivir PK and potential accumulation of cyclodextrin. Active form of remdesivir is highly intracellular concentrated and renal impairment does not appear to substantially impact its clearance. The amount of cyclodextrin present is much less than compared to IV voriconazole, and the duration of use is limited to 5 days. Given this, the benefits in many cases likely outweigh risk, thus it is reasonable to continue use for those who start remdesivir and CrCl declines to  $<$  30 mL/min.
  - 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)

### 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)  $\geq$  30 ml/min by local laboratory measure
- Alanine aminotransferase (ALT)  $\leq$  5 x upper limit of normal (ULN) by local laboratory measure

### 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. See attached pages for additional information. Contact site study coordinator for patient referral.

### Evidence Summary for Proposed COVID-19 Therapies

Therapy	Mechanism	Evidence	Comments/Recommendation
Remdesivir	Nucleoside analog: inhibits viral RNA polymerase	<a href="#">In Vitro</a> —low EC <sub>50</sub> value = 0.77 μM <a href="#">Lancet RCT vs. Placebo</a> ; <a href="#">ACTT-1 Results</a> ; <a href="#">Gilead brief</a>	Investigational antiviral, access via emergency use authorization, see below criteria for consideration. Recent in vitro results demonstrate potential antagonism with concurrent hydroxychloroquine.
Corticosteroids	Anti-inflammatory	RECOVER Study – RCT of Dexamethasone 6mg q24h x 10 days vs. supportive care alone: <a href="#">Recovery trial site</a> ; <a href="#">Medrxiv preprint</a>	<b>**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**</b>
ACE-I / ARB	Anti-hypertensives	<a href="#">Theoretical</a> increased viral entry through animal models showing RAAS inhibition leads to ACE-2 upregulation. <b>No evidence to date of a strong association.</b> <a href="#">Kassiri et al.</a> ACE2 knockout mice have adverse ventricular remodeling <a href="#">Oudit et al.</a> ACE-2 downregulation associated with myocardial dysfunction during SARS-CoV-1 <a href="#">Zhang P, et al.</a> Retrospective analysis of ACEi/ARB use	<b>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.</b>  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.
NSAIDs	Anit-inflammatory, analgesic, anti-pyretic	<a href="#">Uncontrolled case report of 4 patients</a> 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.	<a href="#">EMA</a> , <a href="#">FDA</a> and <a href="#">WHO</a> 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. <a href="#">Recent evidence</a> not supportive of initial concern with worse COVID-19 related outcomes in patients using NSAID vs. APAP
Baricitinib, ruxolitinib, acalabrutinib, other TKIs	Janus kinase (Jak) inhibitor AAK1 inhibition impacting viral entry and anti-inflammatory	<a href="#">Theoretical</a> , no clinical evidence available presently. <a href="#">Ruxolitinib</a> pilot RCT results <a href="#">Acalabrutinib</a> 19 patient observational report	Insufficient evidence to recommend use presently outside of clinical trial.
IVIG	Neutralizing antibodies, immunomodulating effects	<a href="#">Cao et al. case report, n=3</a>	Presence of neutralizing antibodies not expected, theoretical immunomodulating effects. <a href="#">SCCM guidelines</a> recommend against use.
Convalescent serum	Neutralizing SARS-CoV-2 specific IgG from recovered patients	<a href="#">Shen, et al. 2020</a> —case report, n=5 patients.	<a href="#">FDA</a> allowing EIND use. Access only through trials, available at all UHealth facilities.
Interferon	Direct viral effects and indirect stimulation of innate immune responses against viral infection	Mostly reports of <a href="#">combination use</a> with ribavirin or LPV/r from China. <a href="#">INTEEREST</a> trial—INF β1b had no effect on mortality in ARDS but increased mortality in subgroup when used w/ steroids	No direct comparison studies in SARS-CoV-2. Recommend against routine use. <a href="#">SCCM</a> guidelines do not recommend.
Statins	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.
Favipiravir	RNA polymerase inhibitor	<a href="#">In Vitro</a> EC50 higher than remdesivir and CLQ/HCLQ <a href="#">Cai et al. 2020</a> —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.

Zinc	Unclear, inhibits viral replication	No published studies, theoretical	Recommend against routine use
Vitamin C	Unclear, likely immunomodulating	No published evidence, ongoing high-dose IV study in China	Low quality evidence, recommend against routine use
Colchicine	Anti-inflammatory, reduces the production of active IL-1 $\beta$	<a href="#">Deftereos et al.</a> 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.
Tocilizumab and other IL-6 antagonists	IL-6 receptor antagonist  Theoretical management of patients with hyperinflammatory response (aka cytokine release)	<u>Case series</u> (n=20), described rapid improvement in patients from oxygenation and inflammatory markers after 400mg dose. Only 2 patients were intubated at time.  <u>Price et al.</u> – Retrospective observational cohort of 153 tocilizumab patients, showed similar survival despite higher inflammatory markers than controls.  <u>Guaraldi et al.</u> – 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  <u>The Regeneron sponsored trial has been terminated due to lack of efficacy and evidence of potential harm.</u>	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.  <b>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.</b>  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.
Hydroxychloroquine (HCLQ)/Chloroquine (CLQ)	Anti-inflammatory and inhibition of viral entry	In Vitro—HCLQ EC <sub>50</sub> = 0.72 $\mu$ M & CLQ EC <sub>50</sub> = 5.47 $\mu$ M  Clinical:	Multiple negative studies among hospitalized patients and those for secondary prophylaxis. <u>Hydroxychloroquine is not recommended for use</u>  <u>NIH halts trials</u> for hydroxychloroquine  Many clinical trials with hydroxychloroquine have terminated at request of DSMBs for lack of efficacy observed in analysis of these trials
<u>HIV Protease Inhibitors:</u>	Inhibition of viral protease	“ LPV/r: in vitro extrapolated from SARS-CoV-1 and MERS-CoV. · <u>Chu-2004</u> and <u>Chan-2003</u> retrospective SARS-CoV-1 · NEJM prospective study of LPV/r vs. supportive care “ DRV/c— <u>Janssen</u> , found no relevant in vitro activity “ ATV—no in vitro studies, but reports that models show high affinity for <u>docking</u>	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.  · Significant drug interactions · Monitor: QTc, liver impairment, cytopenias
Ribavirin (RBV)	Nucleoside analog: inhibits viral RNA polymerase	In vitro EC <sub>50</sub> = 109.5 $\mu$ M  <u>No clinical evidence</u> for SARS-CoV-2, some combination with LPV/r or IFN evidence from SARS-CoV-1	Not recommended as monotherapy, might consider in combination with LPV/r, but unclear role. Use with caution given safety (anemia, teratogenicity). Enteral route preferred.
Nitazoxanide (NTZ)	Unclear, potentially interaction with host regulated pathways	<u>In vitro only</u> , EC <sub>50</sub> = 2.12 $\mu$ M  Evidence in flu with shorter symptom length	Insufficient evidence for routine use, might be considered if other therapies unavailable. Well-tolerated, \$\$\$, suggested dose 1,000mg P O BID
Azithromycin	Antibacterial and proposed anti-inflammatory effects	No in vitro antiviral effects published	Low quality evidence. Combination not recommended outside concern for atypical pneumonia. Monitor QTc closely. Not recommended for use

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 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 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

Floor Patients	D-dimer <1500 AND	D-dimer > 1500* OR
	TEG (MA) ≤ 70 <sup>&amp;</sup> (If available)	TEG (MA) > 70 <sup>&amp;</sup> (If available)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 30 mg BID
Weight 100-150 kg	Enoxaparin 30 mg BID	Enoxaparin 40 mg BID
Weight > 150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min) <sup>#</sup>	UFH 5000 U TID	UFH 7500 U TID

ICU patients	D-dimer <1500 AND	D-dimer 1500* OR
	TEG (MA) ≤ 70 <sup>&amp;</sup> (If available)	TEG (MA) > 70 <sup>&amp;</sup> (If available)
Weight <100 kg	Enoxaparin 40 mg QD	Enoxaparin 40 mg BID
Weight 100-150 kg	Enoxaparin 40 mg BID	Enoxaparin 0.5 mg/kg BID
Weight > 150 kg	Enoxaparin 60 mg BID	Enoxaparin 0.5 mg/kg BID
AKI (GFR<30 ml/min) <sup>#</sup>	UFH 5000 U TID	UFH 7500 U TID

\* 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.

<sup>#</sup> 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

### UCH Ongoing Clinical Trials for COVID-19

Study	Intervention	Study design	Eligible time to enrollment	Inclusion	Exclusion	Risks	Benefits	Considerations	Study Team Contacts
<b>Convalescent Plasma</b> (PI: Beckham/Chauhan)	1-2 units based on weight	Open label	No limit	Age $\geq$ 18, moderate disease (dyspnea, RR $>$ 30, spO <sub>2</sub> $<$ 93%), severe disease (moderate criteria + radiographic evidence of $>$ 50% pulm involvement, supplementary O <sub>2</sub> to maintain spO <sub>2</sub> $>$ 90%), or life-threatening disease (includes NIV, intubation, prone positioning to support O <sub>2</sub> , MOD)	Patient does not accept blood products.	infection, TRALI, thrombophilia	proposed anti-viral properties	Consider risk of transfusion. May exclude participation in other studies. Currently, no evaluation for neutralizing antibodies prior to administration.	David Beckham, MD (PI)  <b>Contact for enrollment:</b> Lakshmi Chauhan, MD
<b>Ruxolitinib</b> (sponsor: Novartis; PI Campbell)	Roxolitinib 5mg PO bid x 14 days vs placebo	Randomized double-blind placebo-controlled (1:1)	N/A	Age $\geq$ 12, confirmed SARS-CoV-2 infection, hospitalized, chest imaging with pulm infiltrates, O <sub>2</sub> sat $\leq$ 93% on RA (NOT intubated or in ICU)	Other active infection, current or hx of active TB, hx of PML, other anti-rejection/immunosuppressive drugs, chronic steroids $>$ 10mg/d, SCr $>$ 2 or CrCl $<$ 30, ALT $\geq$ 5x ULN, ANC $<$ 1000, plt $<$ 50, liver cirrhosis, pregnant, intubated, participation in other investigational trials.	Risk of infection. Risk of LFT elevation and cytopenias.	Potentially reduces inflammatory response	Pts must be on the floor at time of enrollment (not intubated or in ICU). If pt gets intubated after enrollment, medication can be given via NGT.  <u>Prohibited meds:</u> other JAK inhibitor, aspirin $>$ 150mg/d, fluconazole $>$ 200mg daily	<b>Contact for enrollment:</b> Thomas Campbell, MD
<b>tPA</b> (PI: Moore)	50mg vs 100mg vs SOC	Pragmatic, open label, randomized controlled	N/A	Age 18-75, mechanically ventilated with ARDS (P/F $<$ 150),	Active bleeding or high risk for bleeding, including CNS bleed (see study document for details); Cr	Risk of major bleeding events	Potential improvement in pulmonary gas exchange	Patients concurrently enrolled in other COVID-19	

				neuro exam without focal or new deficits or MRI/CT within 4.5 hrs without e/o stroke	>3x baseline, ALT >3x baseline, HD instability on norepi >0.2, ECMO		and oxygenation via decrease in pulmonary vascular microthrombi	therapeutic trials are eligible, as long as the other trials allow co-enrollment as well.	
<b>Monoclonal antibody – inpatient study</b>  (Sponsor: Regeneron PI: Campbell)	REGN10933+REGN10987 2.4g IV once vs. 8g IV once vs. placebo IV once	Adaptive, phase 1-3, randomized, double-blind, placebo controlled study	≤ 7 days from symptom onset and ≤ 72 hours hospitalization and since SARS-CoV-2 NAAT (can retest if done PTA)	≥ 18 years, O2 saturation <93% on NC or facemask,  -Can get EUA remdesivir or anti-IL6 therapy	High-intensity O2 (HHFNC or MV), CRRT, ECMO, Shock (low dose vasopressors ok), new onset stroke or seizure during hospitalization, convalescent plasma or IVIG in past 6 months, participation in other double-blind trials, pregnant or breast-feeding women		Blockade of host cell entry by neutralizing antibodies against spike protein could be an effective treatment of COVID-19. REGN10933 and REGN10987 are fully human monoclonal antibodies that bind spike protein and prevent entry of the virus into cells.		<b>Contact for enrollment:</b> Thomas Campbell, MD
<b>Monoclonal antibody – outpatient study</b>  (Sponsor: Regeneron PI: Campbell)			≤ 7 days from symptom onset and ≤ 72 hours hospitalization and since SARS-CoV-2 NAAT	At least one symptom (fever, cough, SOB)	Has been admitted or is presently hospitalized for COVID-19, study participation using convalescent plasma, monoclonal antibodies, or IVIG within 3 months, history of COVID-19 investigational or EUA approved treatments in past 30-days (including remdesivir, hydroxychloroquine, tocilizumab, sarilumab), Current use of any COVID-19 investigational or EUA approved treatments				



<p><b>Vaccine</b> (Sponsor: Moderna PI: Campbell)</p>	<p>mRNA-1273 vaccine 100mcg IM injection on day 1 and day 29  vs.  matching placebo IM injection on day 1 and 29</p>	<p>Phase 3, Randomized, Stratified, Observer-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Immunogenicity of mRNA-1273 SARS-CoV-2 Vaccine in Adults Aged 18 Years and Older</p>	<p>No acute illness or fever in 72 hours prior to enrollment</p>	<p>Healthy adults 18 years and older, pre-existing medical conditions are in stable condition, high risk of SARS-CoV-2 infection, able to comply with study procedures</p>	<p>Pregnant or breast feeding, known history of SARS-CoV-2 infection, prior administration of investigational coronavirus vaccine, acutely ill or febrile 72 hours prior to screening</p>	<p>Side effects</p>	<p>Possible protection against SARS-CoV-2 infection</p>	<p>Females of childbearing potential need a negative pregnancy test at screening and day 1 of first dose, practice adequate contraception or abstinence for at least 28 days prior to first dose, and agree to adequate contraception through 3 months after 2<sup>nd</sup> dose. Males must agree to practice adequate contraception and refrain from sperm donation from the time of 1<sup>st</sup> dose to 3 months after 2<sup>nd</sup> dose.</p>	<p><b>Contact for enrollment:</b> Thomas Campbell, MD</p>
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## Convalescent Plasma

(PI: David Beckham, Lakshmi Chauhan)

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

### Inclusion Criteria:

- Age  $\geq$  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:

Score	0	1	2	3
PaO <sub>2</sub> /FiO <sub>2</sub>	$>400$ mmHg	200-400 mmHg or O <sub>2</sub> $>5$ L/min	100-200 mmHg or mechanical ventilation	Prone ventilation, ECMO
Cardiovascular (Hypotension)	MAP $>70$ mmHg	MAP $< \text{or} = 70$ mmHg	On norepi $< \text{or} = 1$ mcg/kg/min	Norepi $> 0.1$ mcg/kg/min or more than 1 pressor
Renal (S. Creat)	$<1.2$	1.2-2.0	2.0-4.0	$> 4.0$ or on dialysis
Age	$>75$	60-75	40-60	$<40$
Days since admission	$>7$	5-7	3-5	$< 3$
Pregnancy status	No or N/A			Yes
Immunocompromised state- immunosuppressive medications, transplant recipient	No	Immuno-suppressive medications including chemotherapy		Functioning organ transplant

**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.**

## Ruxolitinib

Sponsored by Novartis (PI: Campbell)

**Rationale:** Ruxolitinib is an inhibitor of Janus kinase (JAK)1 and JAK2. In the United States (US), ruxolitinib (JAKAFI®) is approved for the treatment of myelofibrosis, polycythemia vera and steroid refractory acute graft versus host disease (GvHD). COVID-19 patients with severe respiratory disease have clinical features consistent with cytokine release syndrome and may benefit by blocking inflammatory pathways, including inhibition of the JAK/STAT pathway. The purpose of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of inpatients with severe COVID-19 pneumonia.

**Study design / treatment protocol:** Phase 3 randomised, double-blind, placebo-controlled multi-center study. Participants will be assigned at randomization to one of the following treatment arms/groups in a ratio of 2:1: ruxolitinib 5 mg tablets twice daily for 14 days; or matching image placebo tablets twice daily for 14 days.

### Key inclusion criteria:

- Age  $\geq$  12 years
- SARS-CoV-2 infection confirmed by PCR or another rapid test from the respiratory tract
- Currently hospitalized or will be hospitalized
- Lung imaging showing pulmonary infiltrates (chest X-ray or chest CT scan) prior to Randomization
- O<sub>2</sub> sat  $\leq$  93% on room air; NOT intubated or in ICU

### Key exclusion criteria:

- Serum creatinine  $>$  2 mg/dL, or CrCl  $<$ 30 ml/min
- Suspected uncontrolled, active bacterial, fungal, viral, or other infection (besides COVID-19)
- Current or history of active TB
- History of progressive multifocal leukoencephalopathy (PML)
- Currently intubated or intubated between screening and randomization.
- Patients who are on oral anti-rejection, immunosuppressant or immunomodulatory drugs (i.e. tocilizumab, ruxolitinib, canakinumab, sarilumab)
- Chronic systemic corticosteroids  $>$  10mg/day
- Participating in any other Investigational trials
- ALT  $\geq$  5 X ULN or evidence of liver cirrhosis (Child A to C)
- ANC  $<$  1000/ $\mu$ L
- Platelet count  $<$  50,000/ $\mu$ L at Screening
- Pregnant or nursing (lactating) women
- Females of child-bearing potential not willing to use a highly-effective method of contraception

**Prohibited medications.** The following medications are prohibited until treatment discontinuation:

- Concomitant use of another JAK inhibitor
- Aspirin in doses  $>$ 150 mg/day
- Systemic corticosteroids  $>$ 10 mg/day
- Fluconazole  $>$  200 mg daily
- Current therapy with medications that interfere with coagulation or platelet function including but not limited to aspirin and related drugs, heparin, and warfarin (to minimize risk of bleeding). Note: Heparin or Low Molecular Weight Heparin (LMWH) is allowed if used at sub-therapeutic dose

## Monoclonal Antibodies

Sponsored by Regeneron (PI: Campbell)

**Rationale:** The coronavirus spike (S) protein allows the virus to enter human cells and is central to viral infectivity by SARS-CoV-2. Blockade of host cell entry by neutralizing antibodies against spike protein could be an effective treatment of COVID-19. REGN10933 and REGN10987 are fully human monoclonal antibodies that bind spike protein and prevent entry of the virus into cells. The purpose of this study is to evaluate the virologic efficacy of co-administered REGN10933+REGN10987 combination therapy compared to placebo.

**Study design / intervention:** Participants will be randomized in a 1:1:1 allocation ratio to one of the following: REGN10933+REGN10987 2.4 g (1.2 g of each mAb) IV single dose; REGN10933+REGN10987 8.0 g (4.0 g of each mAb) IV single dose; or Placebo IV single dose.

### Some requirements to enter the study:

- Age > 18 years old
- Laboratory-confirmed SARS-CoV-2 infection ≤72 hours (can be repeated if out of window)
- Hospitalized for ≤72 hours
- COVID-19 symptom onset ≤7 days
- O<sub>2</sub> saturation >93% while on nasal canula or facemask supplemental O<sub>2</sub>
- No high-intensity O<sub>2</sub> (HHFNC or mechanical ventilation)
- No CRRT, ECMO or shock (low dose vasopressors OK)
- No new onset stroke or seizure during this hospitalization
- No convalescent plasma or IVIG within past 6 months
- No participation in other double-blind clinical trials
- No pregnant or breast-feeding women
- EUA remdesivir or anti-IL6 therapy is allowed
- Dexamethasone allowed

**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 PaO<sub>2</sub>/FiO<sub>2</sub> 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<sup>9</sup>/L or history of HIT
- 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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