

# YNHHS Treatment Guidance for Hospitalized ADULTS with COVID-19

**Disclaimer:** Remdesivir is the only FDA-approved agent to date. **Updated 12/15/20**  
Treatment data continues to evolve & clinical judgment is warranted

Patient with **confirmed POSITIVE** SARS-CoV-2 by PCR  
**ASSESS ALL PATIENTS ROUTINELY FOR CLINICAL TRIAL ELIGIBILITY** (see Appendix 1)

*\* Please refer to page 3 for additional guidance on ECMO patients*

Oxygen saturation  $\leq$  95% on room air and requiring supplemental oxygen  
or oxygen requirement above home baseline

YES

NO

## Remdesivir x 5 days

if hospital length of stay is  $\leq$ 10 days OR  $\leq$ 10 days  
from nosocomial acquisition  
(or until hospital discharge if length of stay  
< 5 days)

(See Appendix 2 for exclusion criteria)

WITH

## Dexamethasone 6 mg po daily x 7 days

(or until hospital discharge if length of stay  
< 7 days)

Doses > 6 mg/day and durations > 10 days have  
not been shown additional clinical benefit &  
may increase infection risk.

***There are no recommended therapies for patients not  
improving on remdesivir and dexamethasone.***

If no clinical improvement (increasing O2 requirement and/or  
rising CRP) within 24-48 hours of steroid therapy, ***please re-  
assess patient eligibility for clinical trials***  
(see Appendices 1, 2, & 3 for trials and exclusion criteria)

**Consider MICU evaluation if O2  $\geq$  5 L/min  
requirement or hemodynamic instability**

(at YNHH see Appendix 4 for suggested triage guidelines)

SUPPORTIVE CARE &  
EVERY 4 HOUR  
OXYGEN MONITORING

## COVID-SPECIFIC TESTS

- 1) **Baseline & every 24 hours:** CRP, D-dimer
- 2) **Baseline & every 24 hours (for 5 days\*):**  
CBC with differential, BMP, LFTs, Procalcitonin, BNP
- 3) **Baseline and with acute kidney injury (AKI):**  
urinalysis and urine protein/albumin ratio
- 4) **Baseline EKG if not done on admission**
- 5) **Repeat Chest X-Ray:** if clinical deterioration.  
(CXR **not** indicated for discharge or to document  
clinical improvement)

**\*May extend longer if clinically indicated.  
Obtain LFTs daily if on remdesivir**

**YNHH & LMH/WH:** ID consult is not  
mandatory for remdesivir. Make requests for  
remdesivir through a non-formulary/ restricted  
medication consult to pharmacy.  
**BH & GH:** consult ID and non-formulary/  
restricted medication consult for remdesivir  
requests.

Report suspected adverse events related to therapeutics through [RL solutions](#)

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## Anticoagulation Dosing Guidelines (Non-Pregnant Patients)<sup>¥</sup>

D-dimer	Give Aspirin <sup>#</sup> ?	BMI < 40 kg/m <sup>2</sup>	BMI ≥ 40 kg/m <sup>2</sup>
< 5 mg/L Prophylaxis	Yes	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 40mg sq daily <u>CrCl &lt; 30mL/min</u> • Enoxaparin 30mg sq daily • Heparin 5000 units sq Q8-12H	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 40mg sq Q12H <u>CrCl &lt; 30mL/min</u> • Enoxaparin 40mg sq Q24H • Heparin 7500 units sq Q8-12H
≥ 5 mg/L or Receiving convalescent plasma Intermediate Dose Prophylaxis	Yes	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 0.5mg/kg sq Q12H* • DOAC <u>CrCl &lt; 30mL/min</u> • Enoxaparin 0.5mg/kg sq Q12H* • DOAC • Heparin 7500 units sq Q8-12H	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 0.5mg/kg sq Q12H* • DOAC <u>CrCl &lt; 30mL/min</u> • Enoxaparin 0.5mg/kg sq Q12H* • DOAC • Heparin 7500 units sq Q8H
Confirmed VTE with diagnostic imaging <b>TREATMENT<sup>€</sup></b>	No	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 1mg/kg sq Q12H • DOAC <u>CrCl &lt; 30mL/min</u> • Enoxaparin 1mg/kg sq Q24H • DOAC • Therapeutic heparin	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 1mg/kg sq Q12H • DOAC <u>CrCl &lt; 30mL/min</u> • Enoxaparin 1mg/kg sq Q24H • DOAC • Therapeutic heparin

DOAC	D-dimer ≥ 5 mg/L Intermediate Dose Prophylaxis	Confirmed VTE treatment with diagnostic imaging
Apixaban	5mg PO Q12H regardless of renal function	10mg PO Q12H x 7 days followed by 5mg PO Q12H (limited data for 10mg in CrCl < 25 or Cr > 2.5) Do not give loading dose if patient has been on 7 days of therapeutic anticoagulation
Rivaroxaban (may favor in BMI ≥ 40kg/m <sup>2</sup> )	20mg Q24H Avoid use with CrCl < 30mL/min	15mg PO Q12H x 21 days followed by 20mg PO Q24H Avoid use with CrCl < 30mL/min Do not give loading dose if patient has been on 21 days of therapeutic anticoagulation
Comment	Administer Aspirin <sup>#</sup>	NO Aspirin

<sup>¥</sup>Enoxaparin is the preferred form of anticoagulation

<sup>#</sup>Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication

<sup>◇</sup>Relative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

\*Target anti-Xa levels between 0.3 – 0.7 units/mL

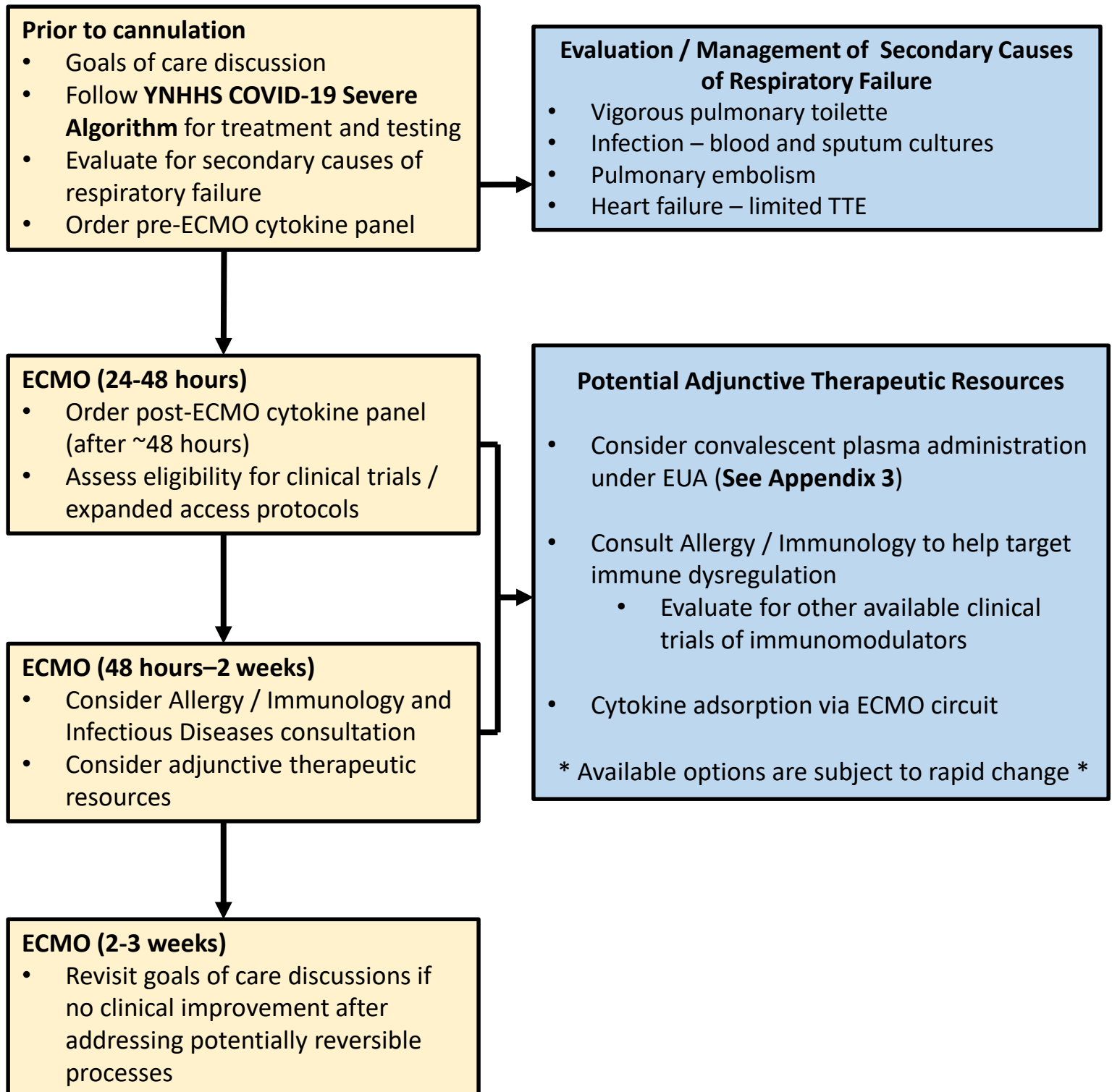
<sup>€</sup>Patients receiving treatment should continue full dose anticoagulation for 3 months

Consult pharmacy for assistance with dosing recommendations, if needed. Seek hematology input for further recommendations on treatment as needed

**For anticoagulation management in PREGNANT patients and at discharge see appendix 5a & 5b**

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## Guidance for Patients with Confirmed COVID-19 and Refractory Respiratory Failure Requiring ECMO



## Appendix 1: Active Coronavirus (SARS-CoV)-2 infection Clinical Trials for Hospitalized Patients

Drug, study description and rationale for use	Inclusion and Exclusion Criteria		Notable adverse effects	Primary Investigator(s)/ Contact Information
<p><b>Drug: Remdesivir (RDV)</b> Broad-spectrum nucleotide prodrug which inhibits RNA polymerase activity against pathogenic coronaviruses.</p> <p><b>Tocilizumab (TCZ)</b> Monoclonal antibody which inhibits soluble and membrane-bound IL-6R</p> <p><u>Rationale</u> Remdesivir and tocilizumab have been well-tolerated in patients with severe COVID-19 pneumonia. Combined RNA nucleotide antagonism via remdesivir and inhibition of pro-inflammatory states via tocilizumab in patients with severe COVID-19 pneumonia may lend improved effectiveness.</p> <p><u>Description</u> Phase III, randomized, double-blind trial in which patients will be randomized 2:1 to receive either remdesivir plus tocilizumab or remdesivir plus placebo.</p> <p>Patients assigned to the RDV + TCZ arm will receive remdesivir as a 200 mg IV loading dose followed by one infusion of tocilizumab 8 mg/kg or placebo (maximum dose of 800 mg) on Day 1. Patients will subsequently be administered a 100 mg once-daily IV maintenance dose of remdesivir from Days 2-10 (or</p>	Inclusion	<ul style="list-style-type: none"> <li>• Informed consent or assent (depending on age)</li> <li>• Aged ≥ 12 years hospitalized with COVID-19 pneumonia confirmed by PCR and evidenced by Chest X-ray to CT scan (PCR must be ≤ 7 days before randomization)</li> <li>• Requiring &gt; 6L/min supplemental oxygen to maintain SpO2 &gt; 93%</li> <li>• Agreement not to participate in another COVID-19 treatment trial while participating</li> <li>• Ability for men and women of childbearing potential to adhere to contraception rules</li> </ul>	<p>Remdesivir: infusion reactions, elevated LFTs, kidney toxicity (dose-dependent and reversible), possible viral resistance</p>	<p>YNHH PI: Onyema Ogbuagu Lead CRC: Laurie Andrews <a href="mailto:laurie.andrews@yale.edu">laurie.andrews@yale.edu</a></p>
Exclusion	<ul style="list-style-type: none"> <li>• If progression to death is imminent and inevitable within next 24hrs</li> <li>• Suspected active bacterial, fungal, viral, or other infection besides COVID-19</li> <li>• Allergy to tocilizumab or other monoclonal antibodies or remdesivir</li> <li>• Active TB infection</li> <li>• Treatment with immunosuppressive/modulators in past 3 months</li> <li>• Participation in another drug clinical trial</li> <li>• eGFR &lt; 30mL/min/1.73m<sup>2</sup></li> <li>• ALT or AST &gt; 5x ULN</li> <li>• ANC &lt; 1000/uL</li> <li>• PLT &lt; 50,000/uL</li> <li>• Weight &lt; 40kg</li> <li>• Pregnant/breastfeeding</li> <li>• Treatment with investigation drug with 5 half-lives or 30 days or randomization</li> </ul>	<p>Tocilizumab: infusion reactions, serious infections and opportunistic infections, GI perforations, hematological malignancies, demyelinating disorders, elevated LFTs</p>		

<p>at time of hospital discharge of 10 days have not been completed).</p>				
<p><b>Convalescent plasma</b> in COVID-19 patients</p> <p><u>Rationale:</u> Use of convalescent plasma is a form of passive antibody therapy that involves the administration of antibodies to a given agent to a susceptible individual for the purpose of potentially treating COVID-19.</p> <p><u>Description:</u> Randomized, blinded phase 2 study evaluating the safety and efficacy of convalescent plasma compared to placebo in hospitalized patients with COVID-19</p>	<p>Inclusion</p>	<ul style="list-style-type: none"> <li>• Patients ≥18 years of age</li> <li>• Hospitalized with COVID-19 with respiratory symptoms, cough, chest pain, shortness of breath, fever, or oxygen saturation ≤ 94%, or abnormal imaging</li> <li>• Hospitalized for less than 72 hours OR within day 3 to 7 days from first signs of illness</li> <li>• Laboratory confirmed COVID-19</li> <li>• On supplemental oxygen, non-invasive ventilation or high-flow oxygen</li> <li>• Patients may be on other randomized controlled trials of pharmaceuticals for COVID -19 and patients who meet eligibility criteria will not be excluded on this basis.</li> </ul>		<p><u>Clinical Trial Currently only at YNHH Contacts :</u> YNHH : <a href="mailto:Mahalia.desruisseaux@yale.edu">Mahalia.desruisseaux@yale.edu</a></p>
<p><b>Drug: Tofacitinib</b> Selective JAK1 and JAK3 inhibitor</p> <p><u>Rationale:</u> SARS-CoV-2 may manifest cytokine release syndrome. Tofacitinib functions as an intracellular JAK1/JAK3 inhibitor, leading to inhibition of a number of downstream inflammatory, thus potentially decreasing clinical severity of cytokine release syndrome</p> <p><u>Description:</u> Randomized, double blinded, placebo controlled Phase 2b study in patients with SARS-CoV-2 and pneumonia who require supplemental oxygen and have serologic markers of inflammation but do not need mechanical ventilation.</p>	<p>Exclusion</p>	<ul style="list-style-type: none"> <li>• Receipt of pooled immunoglobulin in past 30 days</li> <li>• Contraindication to transfusion or history of prior reactions to transfusion blood products</li> <li>• Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)</li> <li>• Volume overload secondary to congestive heart failure or renal failure</li> <li>• Intracranial bleed</li> </ul>	<p>URTI, viral infections, herpes simplex.</p> <p>Joint/muscle/ligament swelling/pain</p>	<p>YNHH PI: Hyung Chun <a href="mailto:hyung.chun@yale.edu">hyung.chun@yale.edu</a></p> <p>Clinical Research Assistant: Danielle Peterson</p>

<p>Will be recruited to tofacitinib or placebo 2:1 and given 10mg PO BID until return to their clinical baseline and will subsequently continue on 5 mg PO BID for a total duration of therapy of 14 days</p>		<ul style="list-style-type: none"> <li>○ Known tuberculosis or inadequately treated tuberculosis</li> <li>○ Known HBV, HCV, or HIV.</li> <li>● Prior/Concomitant Therapy <ul style="list-style-type: none"> <li>○ Within 4 weeks prior to first dose: Prior treatment with any JAK inhibitors, potent immunosuppressants, or any biologic agents including IL-6 inhibitors (eg, tocilizumab) or IL-1 inhibitors (eg, anakinra) within the past 28 days or 5 half-lives, whichever is longer. Prior treatment with any potent cytochrome P450 inducer, such as rifampin, within the past 28 days or 5 half-lives, whichever is longer</li> <li>○ Within 48hrs prior to first dose: treatment with corticosteroids equivalent to prednisone 20mg/day or treatment with herbal supplements</li> </ul> </li> <li>● Diagnostic Assessment <ul style="list-style-type: none"> <li>○ Severe hepatic impairment, defined as Child-Pugh class C.</li> <li>○ Hgb &lt;8 g/dL</li> <li>○ WBC &lt; 1000/mm<sup>3</sup>, absolute lymphocyte count &lt; 500 cells/mm<sup>3</sup>, absolute neutrophil count &lt;1000 cells/mm<sup>3</sup></li> <li>○ ALT/AST &gt; 5 x ULN</li> <li>○ eGFR &lt; 40mL/min/1.73m<sup>2</sup></li> </ul> </li> <li>● Allergy to tofacitinib</li> <li>● Enrollment in another clinical trial to study COVID-19</li> </ul>		
<p><b>I-SPY COVID-19</b>  <b>Drugs:</b>  1. Cenicriviroc: CCR2/CCR5 inhibitor  2. Apremilast/Otezla: PDE4 inhibitor  3. Icatibant: B2 receptor inhibitor, with an affinity similar to bradykinin  4. Razuprotafib: inhibition of vascular endothelial-protein tyrosine phosphatase</p> <p><u>Rationale &amp; Description:</u> SARS-CoV-2 may manifest as ARDS and cytokine release syndrome. I-SPY COVID is an adaptive trial that enrolls severely ill COVID-19 subjects into a “backbone” control arm consisting of standard of</p>	<p><b>Inclusion/Exclusion</b></p>	<p><b>Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>● Male or Female, at least 18 years old</li> <li>● Admitted to the hospital 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</li> <li>● Informed consent provided by the patient or health care proxy</li> <li>● Confirmation of SARS-CoV-2 infection by PCR prior to randomization</li> </ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>● Pregnant or breastfeeding women</li> <li>● 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;</li> <li>● Comfort measures only</li> <li>● Acute or chronic liver disease with a Child-Pugh score &gt; 11</li> <li>● Resident for more than six months at a skilled nursing facility</li> </ul>		<p>YNHH PI: Jon Koff  <a href="mailto:Jon.koff@yale.edu">Jon.koff@yale.edu</a>  RC: Jacqueline Prinz  <a href="mailto:Jacqueline.prinz@yale.edu">Jacqueline.prinz@yale.edu</a></p>

<p>care plus remdesivir and dexamethasone. Each additional study arm is an intervention that is evaluated for safety and efficacy via rolling DSMB review.</p>		<ul style="list-style-type: none"> <li>• Estimated mortality greater than 50% over the next six months from underlying chronic conditions</li> <li>• Time since requirement for high flow oxygen or ventilation greater than 72 hours</li> <li>• Anticipated transfer to another hospital which is not a study site within 72 hours</li> </ul> <p>Patients with either end-stage kidney disease or acute kidney injury who are on dialysis</p>		
<p><b>Investigation of IRAK4 Inhibition to Mitigate the Impact of COVID-19 in Severe SARS-CoV-2 (I-RAMIC)</b></p> <p><u>Rationale:</u> Assess the efficacy of PF-06650833 in addition to standard-of-care compared to standard-of-care treatment alone in improving outcomes in patients with COVID-19.</p> <p><u>Description:</u> Randomized placebo controlled trial comparing 200 mg IR suspension formulation of PF-06650833 every 6 hours (via nasogastric [NG] tube, orogastric [OG] tube, or equivalent) if unable to take tablets by mouth (PO) in addition to standard of care compared to placebo with standard of care.</p>	<p><b>Inclusion/ Exclusion</b></p>	<p><b>Inclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Adult male and female patients, including women of childbearing potential, at least 18 years of age, inclusive</li> <li>• Participant (or legally authorized representative) capable of giving signed informed consent</li> <li>• Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection</li> <li>• Clinical findings and an imaging study consistent with ARDS;</li> <li>• PaO<sub>2</sub> / FiO<sub>2</sub> ratio &lt; 300;</li> <li>• A requirement for mechanical ventilation ≤ 48 hours prior to enrollment.</li> <li>• Evidence of increased inflammation as assessed by hsCRP &gt; ULN AND at least ONE of the following being &gt; upper limit of normal (as available): <ul style="list-style-type: none"> <li>○ Ferritin</li> <li>○ Procalcitonin</li> <li>○ D-dimer</li> <li>○ Fibrinogen</li> <li>○ LDH</li> <li>○ PT/PTT</li> </ul> </li> </ul> <p><b>Exclusion Criteria</b></p> <ul style="list-style-type: none"> <li>• Suspected or known active systemic bacterial, viral (except SARS-CoV2 infection), or fungal infections</li> <li>• Active herpes zoster infection</li> <li>• Known active or latent tuberculosis (TB) or history of inadequately treated TB</li> <li>• Active hepatitis B or hepatitis C</li> <li>• Known history of human immunodeficiency virus (HIV) infection with a detectable viral load or CD4 count &lt; 500 cells / mm<sup>3</sup> (patients for whom documented viral load or CD4 counts are available will be excluded)</li> <li>• Active hematologic cancer</li> <li>• Metastatic or intractable cancer</li> <li>• Pre-existing neurodegenerative disease</li> </ul>		<p>YNHH PI: Hyung Chun <a href="mailto:hyung.chun@yale.edu">hyung.chun@yale.edu</a></p> <p>Clinical Research Assistant: Danielle Peterson</p>

	<ul style="list-style-type: none"> <li>• Severe hepatic impairment defined as Child-Pugh Class B or Class C at baseline</li> <li>• Severe renal impairment with an estimated glomerular filtration rate (eGFR) &lt; 45 mL/min/1.73 m<sup>2</sup></li> <li>• Severe anemia (Hb &lt; 8.0 g/dL)</li> <li>• Any of the following abnormal laboratory values: <ul style="list-style-type: none"> <li>○ absolute lymphocyte count &lt;250 cells/mm<sup>3</sup></li> <li>○ absolute neutrophil Count (ANC) &lt;1000 cells/mm<sup>3</sup></li> <li>○ Platelet count &lt;50,000 cells/mm<sup>3</sup></li> <li>○ ALT or AST &gt; 5X ULN, or other evidence of hepatocellular synthetic dysfunction or total bilirubin &gt; 2X ULN</li> </ul> </li> <li>• Any other medical condition or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study</li> <li>• Prohibited concomitant therapy (see section 1.12.7.2)</li> <li>• Pregnancy (a negative urine or serum pregnancy test is required for inclusion)</li> <li>• Immunocompromised patients, patients with known immunodeficiencies or taking potent immunosuppressive agents (e.g., azathioprine, cyclosporine)</li> <li>• Anticipated survival &lt; 72 hours as assessed by the Investigator.</li> <li>• Participation in other clinical trials of investigational treatments for COVID-19</li> <li>• Known history of nephrolithiasis</li> </ul>		
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**For single patient INDs and emergency use, expanded access may be appropriate when all the following apply:**

- Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, to treat the disease or condition
- Patient enrollment in a clinical trial is not possible
- Potential patient benefit justifies the potential risks of treatment
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication

There are several steps necessary when undertaking emergency use of a drug including specific investigator, Sponsor, and FDA requirements. If a provider assesses emergency use of a drug is appropriate, please contact the Yale Human Research Protection Program (HRPP) and the Investigational Drug Service (IDS) (203-688-4872) as soon as possible to get assistance in identifying and navigating the applicable requirements.



## **Appendix 2: Remdesivir, Tocilizumab, COVID-19 Convalescent Plasma and Exclusion Criteria**

- a. Anticipated immediate death (**≤24 hours**) regardless of critical care support
- b. **Cardiac:** NYHA Class IV heart failure; Severe, inoperable multi-vessel coronary artery disease; Cardiac arrest; Recurrent arrests in the current presentation, or unresponsive to defibrillation or pacing, or unwitnessed out-of-hospital cardiac arrest with poor prognosis
- c. **Hepatic:** Cirrhosis with MELD-Na score  $\geq 25$  (in patients who are not transplant candidates), alcoholic hepatitis with MELD-Na  $\geq 30$ , advanced liver cancer
- d. **Neurologic:** Severe dementia leading to dependence in multiple ADLs; Rapidly progressive or end-stage neuromuscular disease
- e. **Oncologic:** Advanced malignancy or high-grade primary brain tumors receiving only palliative treatment with estimated 3 or fewer month prognosis.
- f. **Pulmonary:** Severe, chronic lung disease with baseline oxygen requirement of  $\geq 60\%$  FiO<sub>2</sub>; Primary pulmonary hypertension with NYHA Class III-IV heart failure (and patient refractory to/not a candidate for pulmonary vasodilators)
- g. **Trauma:** Severe trauma; Severe burns: age  $>60$  and 50% of total body surface area affected
- h. **Functional Status:** Dependent in all ADLs due to a progressive chronic comorbid condition

### **Appendix 3: COVID-19 Convalescent Plasma (CP) Inclusion/Exclusion Criteria**

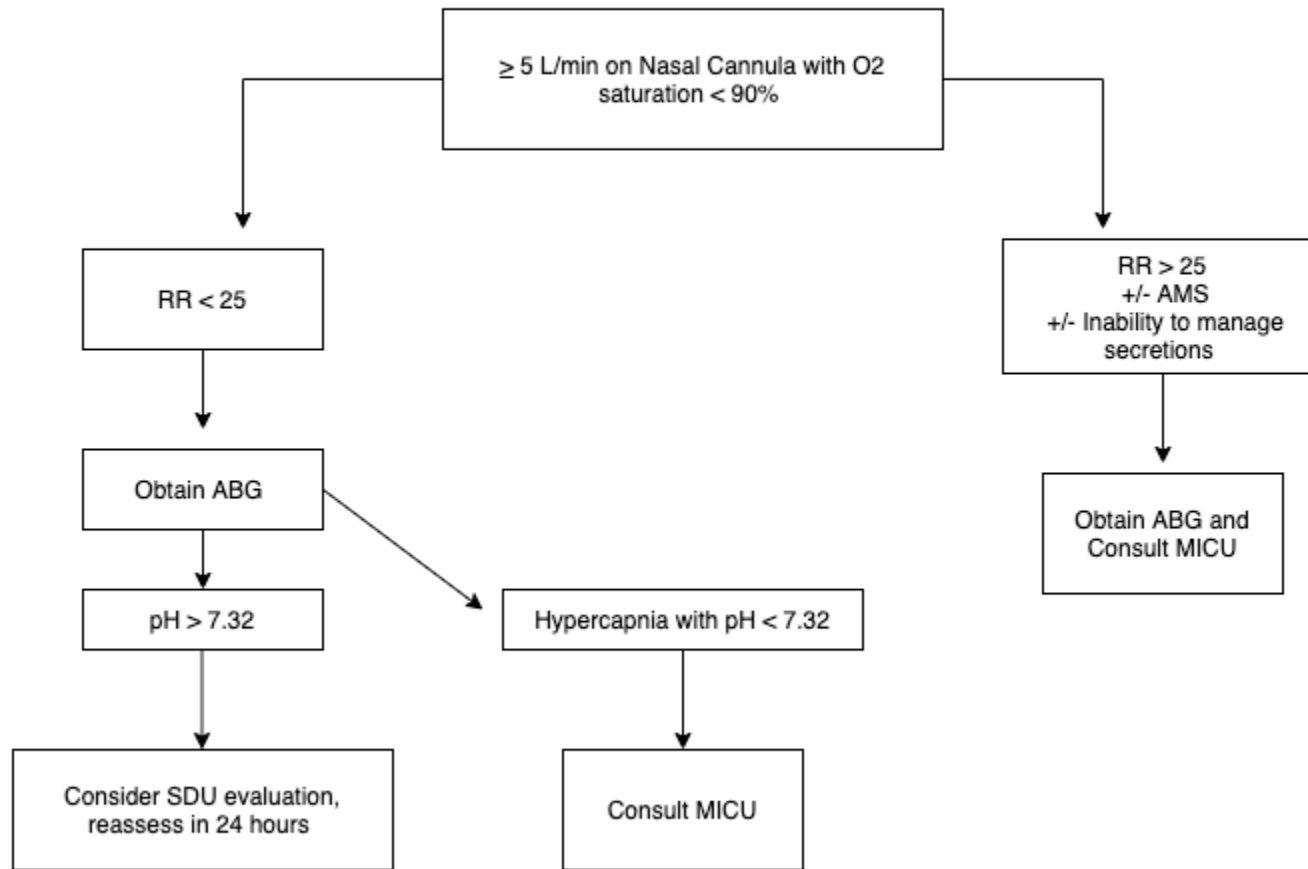
Convalescent Plasma is not stocked in any YNHHS hospital and will take 24 hours to obtain

For patients who **do not meet criteria** for enrollment in the randomized clinical trials (RCT) can receive CP through **emergency use authorization** (EUA) if they meet the following criteria:

1. Patient has a confirmed positive SARS-CoV-2 PCR Result **AND** been admitted for  $\leq 6$  days **AND** requires  $\geq 3$  L of oxygen supplementation
2. Patients who meet the following criteria should be excluded:
  - a. Patient meets any of the exclusion criteria outlined in Appendix 2
  - b. History of anaphylaxis to blood products or history of IgA deficiency
  - c. D-dimer  $> 10$
  - d. Evidence or suspicion of thrombosis
  - e. Active bleed or high risk for bleeding
  - f. Beyond 6 days of hospitalization (from initial admission date)

Any patient who receives CP should receive, at minimum, intermediate dose prophylaxis anticoagulation with enoxaparin for 72 hours, regardless of d-dimer. After 72 hours, the need for intermediate dose prophylaxis can be re-assessed based on d-dimer level and risk for thrombosis. See Appendix 5 with additional anticoagulation recommendations

**Appendix 4: YNHH Acute Respiratory Failure with COVID-19 MICU / SDU Triage Guidelines**



## Appendix 5a: Anticoagulation Dosing Guidelines (Pregnant Patients)

D-dimer	Give Aspirin <sup>#</sup> ?	BMI < 40 kg/m <sup>2</sup>	BMI ≥ 40 kg/m <sup>2</sup>
<b>&lt; 3.5 mg/L Prophylaxis</b>	Yes	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 40mg sq daily</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 30mg sq daily</li> </ul>	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 40mg sq Q12H</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 40mg sq Q24H</li> </ul>
<b>≥ 3.5 mg/L or receiving convalescent plasma Intermediate Dose Prophylaxis</b>	Yes	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 0.5mg/kg sq Q12H*</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 0.5mg/kg sq Q12H*</li> </ul>	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 0.5mg/kg sq Q12H*</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 0.5mg/kg sq Q12H*</li> </ul>
<b>≥ 7 mg/L Confirmed VTE by diagnostic imaging <u>TREATMENT</u></b>	No	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 1mg/kg sq Q12H</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 1mg/kg sq Q24H</li> </ul>	<u>CrCl ≥ 30 mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 1mg/kg sq Q12H</li> </ul> <u>CrCl &lt; 30mL/min</u> <ul style="list-style-type: none"> <li>• Enoxaparin 1mg/kg sq Q24H</li> </ul>

Dosing weight for PREGNANT patients should be actual body weight and POST-PARTUM dosing should be PRE-PREGNANCY weight

<sup>#</sup>Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication

<sup>◇</sup>Relative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

\*Target anti-Xa levels between 0.3 – 0.7 units/mL

Consult pharmacy for assistance with dosing recommendations, if needed. Seek hematology input for further recommendations on treatment as needed, including duration.



## Appendix 5b: Anticoagulation Discharge Recommendations

1. Patients who had initiation of treatment doses during the hospital stay for either presumed or objectively documented venous thrombosis should be discharged on full dose anticoagulation therapy (Direct oral anticoagulant (DOAC), LMWH, warfarin) for a minimum treatment period of three months.
  - We recommend that these patients have follow up with their primary care physician or specialty physician within six weeks of discharge to assess ongoing risk benefit ratio of anticoagulation.
  
2. Patients who received standard dose VTE prophylaxis in hospital should not ordinarily continue with VTE prophylaxis. If, however, they are being discharged to another medical care facility, standards of care at that facility should prevail.
  
3. Patients who received escalated dose (intermediate dose) VTE prophylaxis could be considered for extended VTE prophylaxis with rivaroxaban 10 mg daily for 35 days or LMWH if rivaroxaban cannot be used. The following conditions can be used to determine if a patient is eligible to receive extended duration VTE prophylaxis:
  - Patient should have either:
    1. Modified IMPROVE VTE Risk Score is  $\geq 4$
    2. Modified IMPROVE VTE Risk Score is 2 or 3 and a D-dimer is  $> 2x$  ULN. (D-dimer measured within 24 hours of discharge should be used for this determination)
  - Patient should **NOT** have any of the following:
    1. Major bleeding during hospital stay or during the three months prior to index hospital stay
    2. Major surgery within the last four weeks
    3. Prolonged PT (INR  $> 1.5$ - measured within 24 hours of discharge)
    4. Known bleeding disorder
    5. Current use of anti-platelet therapy
    6. CrCl of  $< 30$  mL/min
    7. Discharge platelet count  $< 100,000/ul$  (measured within 24 hours of discharge)
    8. Other contraindications to anticoagulation with a DOAC

### Calculating the Modified IMPROVE VTE Risk Score

VTE Risk Factor	VTE Risk Score
<b>Previous VTE</b>	3
<b>Known thrombophilia*</b>	2
<b>Current lower limb paralysis or paresis**</b>	2
<b>History of cancer<sup>‡</sup></b>	2
<b>ICU/CCU Stay</b>	1
<b>Complete immobilization <math>\geq 1</math> day<sup>†</sup></b>	1
<b>Age <math>\geq 60</math> years</b>	1

\*A congenital or acquired condition leading to excess risk of thrombosis (factor V Leiden, lupus anticoagulant, factor C or S deficiency)

\*\*Leg falls to bed by 5 seconds, but has some effort against gravity (taken from the NIH stroke scale)

<sup>‡</sup>Cancer (excluding non-melanoma skin cancer) present at any time in the last 5 years (cancer must be in remission to meet criteria)

<sup>†</sup>Immobilization is being confined to bed or chair with or without bathroom privileges

## Appendix 6. Therapies for Hospitalized COVID-19 Patients

(Subject to change as more data becomes available and based on medication availability)

Drug	Dose	Mechanism	Rationale for use	Notable Adverse Reactions	Other considerations
<b>Remdesivir (1-8)</b>	200mg IV once followed by 100mg IV daily for 5 days	<ul style="list-style-type: none"> <li>Viral RNA dependent RNA polymerase inhibitor</li> </ul>	<ul style="list-style-type: none"> <li><i>In-vitro</i> data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit</li> </ul>	<ul style="list-style-type: none"> <li>Nausea, vomiting,</li> <li>Elevated liver enzymes</li> <li>Rectal bleeding</li> </ul>	<ul style="list-style-type: none"> <li>Remdesivir was approved by the FDA on 10/22/20 for COVID-19 treatment.</li> <li>Although there is a FDA-warning regarding remdesivir use in patients with CrCl&lt;30 ml/min due to the accumulation of cyclodextrin, there is a lack of clinical data to suggest this is problematic in this population. Other medications with cyclodextrin have been given in this population without any adverse effects.</li> <li>Therapy should be started with dexamethasone if patients meet criteria as defined on page one.</li> </ul>
<b>Corticosteroids (9-13)</b>	Dexamethasone 6 mg daily for 7 days	<ul style="list-style-type: none"> <li>Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression</li> </ul>	<ul style="list-style-type: none"> <li>Can attenuate cytokine release in patients in patients with severe disease</li> </ul>	<ul style="list-style-type: none"> <li>Hyperglycemia</li> <li>Adrenal suppression and myopathy if given in high doses for long periods</li> <li>Psychiatric disturbances in certain patients</li> <li>Perforation risk in patients with GI disease</li> <li>Fluid retention and hypertension</li> </ul>	<ul style="list-style-type: none"> <li>Lower 28-day mortality was observed in patients receiving invasive mechanical ventilation or oxygen but <b>NOT</b> among those receiving <b>NO respiratory support (13)</b></li> <li>Corticosteroids should be used if clinically indicated as part of standard of care such as for an asthma or COPD exacerbation, or shock with history of chronic steroid use.</li> <li>Patients on steroids at home should be administered dexamethasone at the recommended dose of 6 mg in place of their chronic steroid for the recommended duration and then be re-started on their home steroid. There is a lack of data to support higher dose of steroid in patients on therapy chronically who develop COVID-19.</li> </ul>

					<ul style="list-style-type: none"> <li>Other steroid equivalent can be considered if dexamethasone is not available.</li> </ul>
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### Available Therapy through Clinical Trial or Emergency Use Authorization (EUA)

(Subject to change as more data becomes available and based on medication availability)

<b>Convalescent Plasma (14-18)</b>	One ABO compatible unit	<ul style="list-style-type: none"> <li>Individual (not pooled) plasma from a recovered COVID19 patient</li> </ul>	<ul style="list-style-type: none"> <li>Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis</li> </ul>	<ul style="list-style-type: none"> <li>Transfusion reactions</li> <li>Potential to increase hypercoagulability</li> </ul>	<ul style="list-style-type: none"> <li>Each unit may contain variable titers of anti-SARS-CoV-2 antibodies with differing avidity</li> <li>Cannot be used in patients with IgA deficiency due to risk of anaphylaxis</li> <li>Use with intermediate dosing anticoagulation (see Appendix 5 above)</li> <li>See Appendix 3</li> </ul>
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### Therapy with conflicting data

(Current use is recommended by NIH/IDSA only under clinical trials )

<b>Tocilizumab (19-27)</b>	8mg/kg IV x 1 dose (actual body weight; dose max 800 mg)	<ul style="list-style-type: none"> <li>Monoclonal antibody to IL6 receptor</li> </ul>	<ul style="list-style-type: none"> <li>IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease</li> <li>Retrospective data suggest possible benefit (clinical trials ongoing)</li> </ul>	<ul style="list-style-type: none"> <li>Headache</li> <li>Elevated liver enzymes</li> <li>Infusion reactions (e.g. flushing, chills)</li> </ul>	<ul style="list-style-type: none"> <li>The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time</li> <li>Additional doses not indicated at this time</li> <li>Can be considered 48 hours after remdesivir and dexamethasone <i>if there is no clinical improvement ( increasing O2 requirement and/or rising CRP) AND no available clinical trial or patient is ineligible for clinical trial.</i></li> </ul>
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### Therapy with limited data

(Current use is preferred to be given under clinical trials)

<b>Baricitinib (28, 29)</b>	N/A	<ul style="list-style-type: none"> <li>Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase, may inhibit viral entry via endocytosis</li> </ul>	<ul style="list-style-type: none"> <li>May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Risk of severe infections with use and possible increase of thrombosis</li> </ul>	<ul style="list-style-type: none"> <li>Not available for off label use</li> <li>No published data</li> <li>FDA issued EUA of remdesivir and baricitinib but data of its safety and efficacy are not available.</li> </ul>
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