

YNHHS Treatment Guidance for Hospitalized ADULTS with COVID-19

Disclaimer: Remdesivir is the only FDA-approved agent to date. **Updated 8/16/21**
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)

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

YES

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 7-10 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

Requiring 3-6 L/min O₂ AND hs-CRP > 75 (non-hs-CRP > 7.5) OR \geq 6 L/min (e.g. NRB, HFNC, NIV, MV)?

YES

NPO OR CrCl < 15 mL/min?

YES

Tocilizumab
x 1 dose*
*if available

NO

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

If no clinical improvement (increasing O₂ requirement and/or rising CRP) within 24-48 hours of above therapy or tocilizumab is unavailable, *please assess patient eligibility for clinical trials* (see Appendices 1 & 2 for trials and exclusion criteria).
If hospital length of stay is \geq 7 days, consult Antimicrobial Stewardship/ID (See Appendix 2 for exclusion criteria).

Consider MICU evaluation if O₂ \geq 5 L/min requirement or hemodynamic instability
(at YNHHS see Appendix 3 for suggested triage guidelines)

NO

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 tocilizumab and baricitinib. Make requests for through a non-formulary/ restricted medication consult to pharmacy.
BH & GH: consult ID and non-formulary/ restricted medication consult for tocilizumab/baricitinib requests.

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

Treatment guidance reviewed by YNHHS SAS and YNHHS/YSM Ad-Hoc COVID-19 Treatment Team

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Treatment data continues to evolve & clinical judgment is warranted

Anticoagulation Dosing Guidelines (Non-Pregnant Patients)‡

D-dimer	Give Aspirin#?	BMI < 40 kg/m ²	BMI ≥ 40 kg/m ²
< 5 mg/L Prophylaxis	Yes	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 40mg sq daily <u>CrCl < 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 < 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 < 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 < 30mL/min</u> • Enoxaparin 0.5mg/kg sq Q12H* • DOAC • Heparin 7500 units sq Q8H
Confirmed VTE with diagnostic imaging TREATMENT €	No	<u>CrCl ≥ 30 mL/min</u> • Enoxaparin 1mg/kg sq Q12H • DOAC <u>CrCl < 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 < 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 ²)	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#		NO Aspirin

‡Enoxaparin is the preferred form of anticoagulation

#Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication. Do not continue on discharge unless patient was receiving prior to admission.

◊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

€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 4a & 4b

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>I-SPY COVID-19</p> <p>Drugs:</p> <ol style="list-style-type: none"> 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><u>Rationale & 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 care plus remdesivir and dexamethasone. Each additional study arm is an intervention that is evaluated for safety and efficacy via rolling DSMB review.</p>	Inclusion	<ul style="list-style-type: none"> • Male or Female, at least 18 years old • 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 • Informed consent provided by the patient or health care proxy • Confirmation of SARS-CoV-2 infection by PCR prior to randomization 		<p>YNHH PI: Jon Koff Jon.koff@yale.edu RC: Jacqueline Prinz Jacqueline.prinz@yale.edu</p>
	Exclusion	<ul style="list-style-type: none"> • Pregnant or breastfeeding women • 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; • Comfort measures only • Acute or chronic liver disease with a Child-Pugh score > 11 • Resident for more than six months at a skilled nursing facility • Estimated mortality greater than 50% over the next six months from underlying chronic conditions • Time since requirement for high flow oxygen or ventilation greater than 72 hours • Anticipated transfer to another hospital which is not a study site within 72 hours • Patients with either end-stage kidney disease or acute kidney injury who are on dialysis 		
<p>Investigation of IRAK4 Inhibition to Mitigate the Impact of COVID-19 in Severe SARS-CoV-2 (I-RAMIC)</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>	Inclusion	<ul style="list-style-type: none"> • Adult male and female patients, including women of childbearing potential, at least 18 years of age, inclusive • Participant (or legally authorized representative) capable of giving signed informed consent • Laboratory-confirmed novel coronavirus (SARS-CoV-2) infection • Clinical findings and an imaging study consistent with ARDS; • PaO₂ / FiO₂ ratio < 300; • A requirement for mechanical ventilation ≤ 48 hours prior to enrollment. • Evidence of increased inflammation as assessed by hsCRP > ULN AND at least ONE of the following being > upper limit of normal (as available): 		<p>YNHH PI: Hyung Chun hyung.chun@yale.edu</p> <p>Clinical Research Assistant: Danielle Peterson</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>		<ul style="list-style-type: none"> ○ Ferritin ○ Procalcitonin ○ D-dimer ○ Fibrinogen ○ LDH ○ PT/PTT 		
	<p>Exclusion</p>	<ul style="list-style-type: none"> ● Suspected or known active systemic bacterial, viral (except SARS-CoV2 infection), or fungal infections ● Active herpes zoster infection ● Known active or latent tuberculosis (TB) or history of inadequately treated TB ● Active hepatitis B or hepatitis C ● Known history of human immunodeficiency virus (HIV) infection with a detectable viral load or CD4 count < 500 cells / mm³ (patients for whom documented viral load or CD4 counts are available will be excluded) ● Active hematologic cancer ● Metastatic or intractable cancer ● Pre-existing neurodegenerative disease ● Severe hepatic impairment defined as Child-Pugh Class B or Class C at baseline ● Severe renal impairment with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m² ● Severe anemia (Hb < 8.0 g/dL) ● Any of the following abnormal laboratory values: <ul style="list-style-type: none"> ○ absolute lymphocyte count <250 cells/mm³ ○ absolute neutrophil Count (ANC) <1000 cells/mm³ ○ Platelet count <50,000 cells/mm³ ○ ALT or AST > 5X ULN, or other evidence of hepatocellular synthetic dysfunction or total bilirubin > 2X ULN ● 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 ● Prohibited concomitant therapy (see section 1.12.7.2) ● Pregnancy (a negative urine or serum pregnancy test is required for inclusion) ● Immunocompromised patients, patients with known immunodeficiencies or taking potent immunosuppressive agents (e.g., azathioprine, cyclosporine) ● Anticipated survival < 72 hours as assessed by the Investigator. 		

		<ul style="list-style-type: none"> • Participation in other clinical trials of investigational treatments for COVID-19 • Known history of nephrolithiasis 		
<p>Drug: Ibudilast (MN-166)</p> <p><u>Rationale:</u> Acute Respiratory Distress Syndrome (ARDS) from SARS-CoV-2 may occur due to aberrant and excessive cytokine release. Ibudilast is an orally available drug inhibits the immunoregulatory cytokine Macrophage Migration Inhibitory Factor (MIF) leading to reduced downstream inflammatory signaling, thus potentially reducing the risk for and severity of ARDS. Ibudilast is also a phosphodiesterase inhibitor, particularly PDE 3, 4, 10, and 11, and may reduce platelet aggregation.</p> <p><u>Description</u> Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy, Safety, Tolerability, Biomarkers and PK of Ibudilast (MN-166) in COVID-19 Subjects at Risk for Developing Acute Respiratory Distress Syndrome (ARDS)</p>	Inclusion	<ul style="list-style-type: none"> • Written or verbal informed consent by subject or subject representative • Male or female subjects age 18 to 80 years, inclusive • SARS-CoV-2 infection confirmed with WHO criteria • SpO2 ≤ 92% on room air (RA), RR ≥ 22 breaths per min on RA, and/or requirement for supplemental oxygen • At least 1 risk factor which may put patient at higher risk for more severe illness from COVID-19: (Age ≥ 65, underlying serious heart disease, chronic lung disease, moderate to severe asthma, body mass index ≥ 40, or diabetes) C-reactive protein >35 mg/L 	<p>Ibudilast: Adverse drug reactions are related to GI upset (anorexia, abdominal pain, nausea, vomiting, diarrhea) Others include headache, elevated LFTs, decreased WBC count, and transient ataxia.</p>	<p>YNHH PI: Maor Sauler Lead CRC: Linda Koumpouras maor.sauler@yale.edu 862-668-6341</p>
	Exclusion	<ul style="list-style-type: none"> • Suspected active bacterial, fungal, viral, or other infection besides COVID-19 • Active TB infection • Allergy to Ibudilast • Participation in another COVID-19 clinical trial • Treatment with investigation drug with 5 half-lives or 30 days or randomization • Pregnant/breastfeeding • PLT < 70,000/uL • WBC <2500/uL • Known or suspected immunosuppression with immunosuppressant medications or chemotherapeutic agents • Patient receiving dialysis prior to study • Active primary lung cancer or another metastatic malignancy to the lungs • Moderate to severe liver failure defined by Child-Pugh score of ≥7 • On home ventilator support or continuous domiciliary O2 therapy for baseline lung disease • History of stomach or intestinal surgery or any other condition that could interfere with or is judged by the Investigator to interfere with absorption, distribution, metabolism, or excretion of study drug • Any other serious medical condition or abnormality that, in the Investigator's opinion, would preclude participation in the study 		

<p>Colchicine/Statin for the Prevention of COVID-19 Complications (COLSTAT) Trial</p> <p>Drugs: colchicine and rosuvastatin</p> <p><u>Rationale</u> Combination of colchicine + rosuvastatin may have synergetic effect to antagonize SARS-CoV-2 infection, modulate inflammatory response and reduce morbidity and mortality associated with acute respiratory distress syndrome (ARDS) and myocardial injury in COVID-19 patients. By inhibiting tubulin polymerization and clathrin-mediated endocytosis colchicine has the potential to inhibit SARS-CoV-2 cell entry. Also, colchicine has direct anti-inflammatory effect by inhibiting the NLRP3 inflammasome activation, which in turn has the potential to reduce the SARS-CoV-2-induced cytokine storm. By reducing chemokine release, adhesion molecules, and modulating T cell activity, statins have the potential to prevent SARS-CoV-2 related endothelial dysfunction and may reduce the morbidity and mortality associated with COVID-19. Rosuvastatin, in particular, appears to have direct antiviral properties by binding and inhibiting active site of main protease enzyme (Mpro) of SARS-CoV-2.</p> <p><u>Description</u> Randomized open-label study of the safety and efficacy of combination of colchicine and rosuvastatin in addition to standard of care compared to standard of care alone.</p>	<p>Inclusion</p>	<ul style="list-style-type: none"> • 18 years or older and confirmed SARS-CoV-2 infection by RT-PCR • Patient is admitted to the floor (non-ICU) within 48 hours of hospital admission • The patient, or legally authorized representative, has been informed of the nature of the study, agrees to its provisions and has provided witnessed (by 2 independent members of the health care team) oral informed consent, or a photograph of the signed informed consent approved by the Institutional Review Board (IRB) 	<p>Colchicine: Abdominal pain, nausea, diarrhea, vomiting, rash, elevated AST/ALT, myopathy</p> <p>Rosuvastatin: Myalgia, abdominal pain, nausea, headache</p>	<p>YNHH Principal Investigator: Alexandra J Lansky, MD alexandra.lansky@yale.edu</p> <p>Lead CRC: Marianne McCarthy marianne.mccarthy@yale.edu</p> <p>Greenwich Hospital: Chris Howes, MD Herb Archer, MD Herbert.archer@greenwichhospital.org Irem Nasir, MD Irem.nasir@greenwichhospital.org</p> <p>Bridgeport Hospital: Gil Lancaster, MD Gilead.lancaster@bpthospital.org Faheem Ul Haq, MD Faheem.ulhaq@bpthospital.org Tina McCurry, RN Tina.mccurry@bpthospital.org</p> <p>Lawrence & Memorial Hospital: Brian Cambi, MD Chris Song, MD Christopher.song@lmhospital.org Prakash Kandel, MD Prakash.kandel@lmhospital.org</p>
	<p>Exclusion</p>	<ul style="list-style-type: none"> • Known pregnancy or nursing mothers • Known allergy to statins or colchicine • Patient is on chronic colchicine or oral corticosteroid treatment • Acute liver disease defined by elevated transaminases (AST/ALT > 3x ULN) • Severe chronic kidney disease defined as glomerular filtration rate (GFR) < 30mL/min/1.73 m² • Severe QTc prolongation (>500ms narrow QRS<120ms and >550ms for wide QRS_≥120) • Presents with severe disease on admission (WHO ordinal scale of clinical improvement scores 5-8) • Rhabdomyolysis or CPK > 5x ULN • Thrombocytopenia defined as platelet count < 50,000 / mm³ • Leukopenia defined as white blood cell count < 3000/μl • Severe anemia defined as Hemoglobin value <11g/100ml • Participation in any other clinical trial of an experimental treatment for COVID-19 		

<p>NIH ACTIV-5 Multicenter Platform Trial of Putative Therapeutics for the Treatment of COVID-19 in Hospitalized Adults</p> <p>Drug: Lenzilumab (anti-GMCSF antibody)</p> <p><u>Rationale</u> SARS-CoV-2 infections results in COVID-19 and associated acute respiratory distress syndrome (ARDS) due to dysfunctional and hyperinflammatory immune responses. ACTIV-5 is an NIH multicenter platform trial of therapeutics for the treatment of COVID-19 in hospitalized patients. Lenzilumab is a monoclonal antibody that act to reduce cytokine release syndrome through granulocyte-macrophage colony stimulating factor (GM-CSF).</p> <p><u>Description</u> This is a NIH multi-site randomized, double-blind, placebo-controlled trials using a common assessments and endpoints in hospitalized adults diagnosed with COVID-19. For YNHH (York Street): patient will be enrolled to BET B: Lenzilumab/Remdesivir vs. Placebo/Remdesivir.</p>	<p>Inclusion</p> <p>Exclusion</p>	<ul style="list-style-type: none"> Admitted to a hospital with symptoms suggestive of COVID-19 and requires ongoing medical care. Subject (or legally authorized representative) provides informed consent prior to initiation of any study procedures. Male or non-pregnant female adult ≥ 18 years of age at time of enrollment. Has laboratory-confirmed SARS-CoV-2 Illness of any duration, and requiring supplemental oxygen, mechanical ventilation or ECMO. Women of childbearing potential must agree to either abstinence or use at least one primary form of contraception* not including hormonal contraception from the time of screening through 5 months. Agrees to not participate in another clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 60. <ul style="list-style-type: none"> ALT or AST > 5 times the upper limit of normal. Estimated glomerular filtration rate (eGFR) < 30 mL/min are excluded unless in the opinion of the PI, the potential benefit of receiving remdesivir outweighs the potential risk of study participation. Pregnancy or breast feeding. Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours of enrollment. Allergy to any study medication. Received three or more doses of remdesivir prior to study enrollment. Received two or more doses of > 60 mg of prednisone or equivalent in the 7 days prior to screening. Received small molecule tyrosine kinase inhibitors (e.g., baricitinib, ibrutinib, acalabrutinib, imatinib, gefitinib), in the 4 weeks prior to screening. Received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-IL-1 [e.g., anakinra, canakinumab], anti-IL-6 [e.g., tocilizumab, sarilumab, sitlukimab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening. Received monoclonal antibodies targeting B-cells (e.g., rituximab, and including any targeting multiple cell lines including B-cells) in the 3 months prior to screening. Received GM-CSF agents (e.g., sargramostim) within 2 months prior to screening. Known history of HIV, Hepatitis B (HBV) or untreated hepatitis C (HCV) infection. History of pulmonary alveolar proteinosis (PAP). 		<p>YNHH Principle Investigator: Charles Dela Cruz, MD, PhD, Charles.delacruz@yale.edu</p> <p>Lead CRC: Elizabeth Brown, Elizabeth.brown@yale.edu</p>
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		<ul style="list-style-type: none"> • Has active malignancy, immunodeficiency, uncontrolled opportunistic infection, or uncontrolled cirrhosis. 		
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For single patient INDs and emergency use, expanded access may be appropriate when all the following apply:

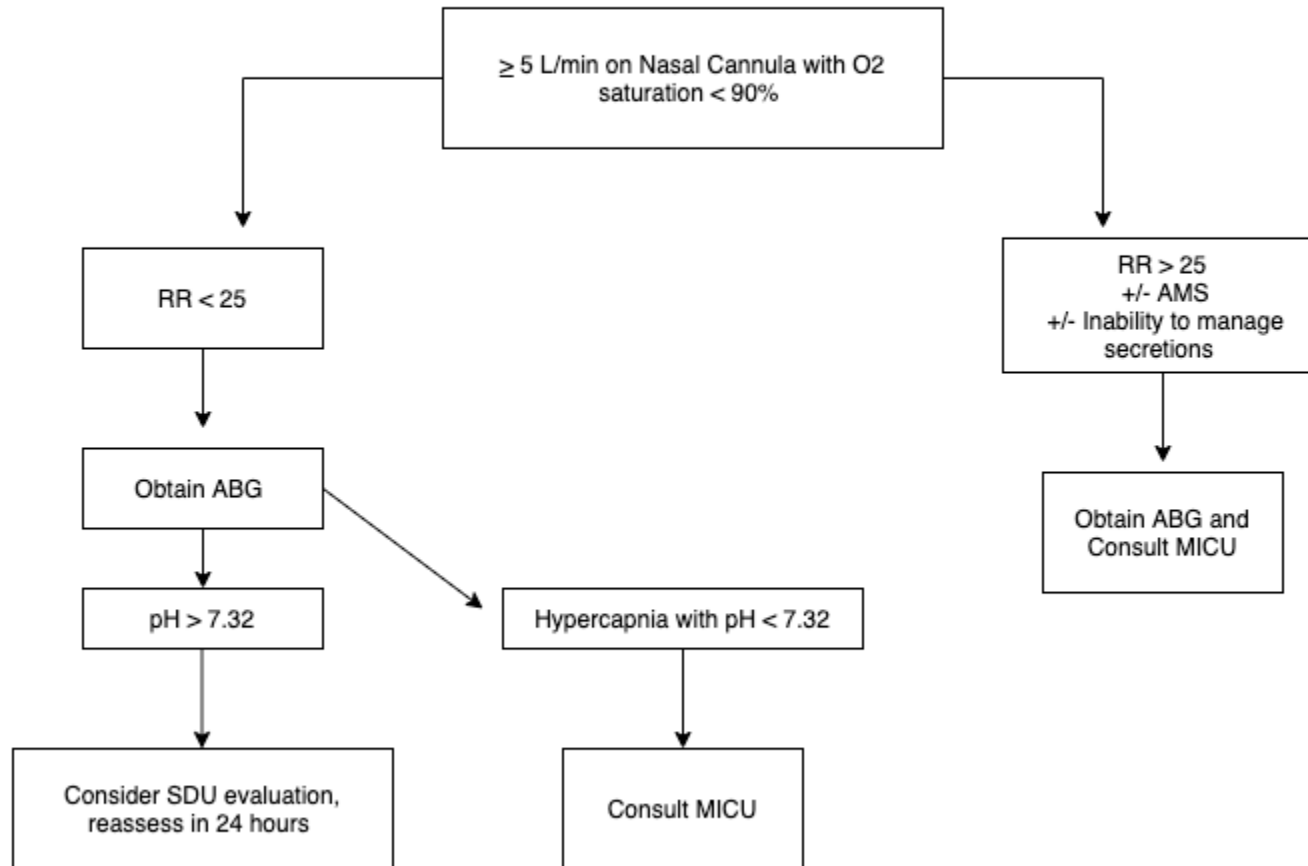
- Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition
- There is no comparable or satisfactory alternative therapy to diagnose, monitor, to treat the disease or condition
- Patient enrollment in a clinical trial is not possible
- Potential 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, and Baricitinib 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 ≥ 25 (in patients who are not transplant candidates), alcoholic hepatitis with MELD-Na ≥ 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 $\geq 60\%$ FiO₂; 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: YNH Acute Respiratory Failure with COVID-19 MICU / SDU Triage Guidelines



Appendix 4a: Anticoagulation Dosing Guidelines (Pregnant Patients)

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

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

[#]Do not give if contraindicated. DO NOT ADMINISTER if patient on therapeutic anticoagulation unless needed for a non-COVID indication

[◇]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 4b: 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 ≥ 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
Previous VTE	3
Known thrombophilia*	2
Current lower limb paralysis or paresis**	2
History of cancer[‡]	2
ICU/CCU Stay	1
Complete immobilization ≥ 1 day[§]	1
Age ≥ 60 years	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)

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

[§]Immobilization is being confined to bed or chair with or without bathroom privileges

Appendix 5. 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
Remdesivir (1-8)	200mg IV once followed by 100mg IV daily for 5 days	<ul style="list-style-type: none"> Viral RNA dependent RNA polymerase inhibitor 	<ul style="list-style-type: none"> <i>In-vitro</i> data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit 	<ul style="list-style-type: none"> Nausea, vomiting, Elevated liver enzymes Rectal bleeding 	<ul style="list-style-type: none"> Remdesivir was approved by the FDA on 10/22/20 for COVID-19 treatment. Although there is a FDA-warning regarding remdesivir use in patients with CrCl<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. Therapy should be started with dexamethasone if patients meet criteria as defined on page one.
Corticosteroids (9-13)	Dexamethasone 6 mg daily for 7 days	<ul style="list-style-type: none"> Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression 	<ul style="list-style-type: none"> Can attenuate cytokine release in patients in patients with severe disease 	<ul style="list-style-type: none"> Hyperglycemia Adrenal suppression and myopathy if given in high doses for long periods Psychiatric disturbances in certain patients Perforation risk in patients with GI disease Fluid retention and hypertension 	<ul style="list-style-type: none"> Lower 28-day mortality was observed in patients receiving invasive mechanical ventilation or oxygen but NOT among those receiving NO respiratory support (13) 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. 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. Other steroid equivalent can be considered if dexamethasone is not available.
Tocilizumab (14-26)	8mg/kg IV x 1 dose (actual body weight; dose max 800 mg)	<ul style="list-style-type: none"> Monoclonal antibody to IL6 receptor 	<ul style="list-style-type: none"> IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease Prospective and retrospective data suggest possible benefit 	<ul style="list-style-type: none"> Headache Elevated liver enzymes Infusion reactions (e.g., flushing, chills) 	<ul style="list-style-type: none"> The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time Additional doses not indicated at this time Risk versus benefit in patients with ALT/AST more than 5 times the upper limit of normal and/or a platelet count of < 50 x10⁹/L

					<ul style="list-style-type: none"> National shortage of tocilizumab which limits availability
Baricitinib (27-31)	<p>Dose based on CrCl</p> <p>Not recommended if CrCl < 15 mL/min</p>	<ul style="list-style-type: none"> Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase, may inhibit viral entry via endocytosis 	<ul style="list-style-type: none"> May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors 	<ul style="list-style-type: none"> Risk of severe infections with use and possible increase of thrombosis Increased LFTs 	<ul style="list-style-type: none"> Given tocilizumab shortage baricitinib can be utilized in place of this agent FDA issued EUA of remdesivir and baricitinib Monitor absolute neutrophil count (ANC) and consider interruption if ANC is < 500 cells/μL Monitor absolute lymphocyte count (ALC) and consider interruption if ALC is < 200 cells/μL Consider interruption if drug induced liver injury suspected

Therapies that are no longer recommended or available

Convalescent Plasma (32-40)	One ABO compatible unit	<ul style="list-style-type: none"> Individual (not pooled) plasma from a recovered COVID19 patient 	<ul style="list-style-type: none"> Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis 	<ul style="list-style-type: none"> Transfusion reactions Potential to increase hypercoagulability 	<ul style="list-style-type: none"> Based on the RECOVERY, REMAP-CAP, and CONCOR-1 trials CCP has not shown to provide benefit for treatment of COVID-19 and therefore is no longer available across YNHHS.
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**Therapy with limited data
(Current use is preferred to be given under clinical trials)**

Tofacitinib (41)	N/A	<ul style="list-style-type: none"> Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase 	<ul style="list-style-type: none"> Immunomodulatory properties via selective inhibition of JAK 1 and 3 and functional selectivity for JAK2 	<ul style="list-style-type: none"> Risk of severe infections with use and possible increase of thrombosis 	<ul style="list-style-type: none"> Not available for off label use at YNHHS. Tofacitinib was studied in hospitalized non-ICU patients and showed a potential decrease in a composite endpoint of death and respiratory failure, however, this was compared placebo and therefore the trial applicability is limited due to the small sample size, the lack of the use of remdesivir and nearly 25% of the patients did not require supplemental oxygen (41).
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Therapy with NO data for Hospitalized Patients
(Current use is preferred to be given under clinical trials)

<p>Ivermectin(42, 43)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Inhibition of SARS CoV-2 viral replication 	<ul style="list-style-type: none"> • In vitro data demonstrated potent inhibition of viral inhibition 	<ul style="list-style-type: none"> • Pruritus, dermatological reaction, lymphadenitis, arthralgia, synovitis, fever 	<ul style="list-style-type: none"> • There is a lack of clinical data to support the use of ivermectin for the treatment of COVID-19 • Although <i>in-vitro</i> data demonstrated potent anti-SARS CoV-2 activity, a randomized clinical trial (43) and meta-analysis did not show benefit of ivermectin for treatment of COVID-19.
<p>Fluvoxamine (44, 45)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • σ-1 receptor agonist (SSRI) 	<ul style="list-style-type: none"> • Potential immune modulation via σ-1 receptor (S1R) antagonism 	<ul style="list-style-type: none"> • Headache, insomnia, drowsiness, dizziness, nervousness, Nausea, diarrhea, xerostomia, anorexia, Ejaculatory disorder, weakness 	<ul style="list-style-type: none"> • There is insufficient evidence to support the use of fluvoxamine for the treatment of COVID-19 in hospitalized patients and it is not currently recommended by national or international guidelines • A randomized trial and a real-world prospective cohort study in non-hospitalized patients (44, 45) found a lower likelihood of clinical deterioration with COVID-19 treated with fluvoxamine compared with placebo, however this study had several limitations including small sample size and potential for bias given primary and secondary endpoints were measured using participants' self-reported responses on surveys.
<p>Colchicine(46, 47)</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Anti-gout agent 	<ul style="list-style-type: none"> • Inhibition of PMN cell migration • Anti-inflammatory and anti-viral properties 	<ul style="list-style-type: none"> • Gastrointestinal side effects 	<ul style="list-style-type: none"> • The use of colchicine for the treatment of COVID-19 in hospitalized patients is not currently recommended by national or international guidelines (26, 48) • The RECOVERY trial has closed recruitment to colchicine alone for patients hospitalized with COVID-19 given lack of benefit seen in interim analysis(49) . • The COLCORONA phase III trial (46) to evaluate the efficacy and safety of colchicine for 30 days in adult outpatients diagnosed with COVID-19

					<p>infection which showed a mild potential decrease in the composite endpoint of hospitalization and death is now in preprint; however further peer reviewed studies are needed to verify these findings. Of note, there were also a large number of patients who developed gastrointestinal adverse effects from this therapy in the trial as well. Therefore, it is unclear if this potential benefit outweighs the adverse effects from treatment.</p> <ul style="list-style-type: none"> The GRECCO-19 trial (47) was a small prospective open-label study in hospitalized patients that showed patients in the colchicine arm were less likely to reach the clinical endpoint of deterioration and were more likely to experience diarrhea, however, the sample size was low with only ~ 50 patients in each arm.
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