YNHHS Treatment Guidance for Hospitalized ADULTS with COVID-19

Disclaimer: Remdesivir is the only FDA-approved agent to date. Updated 2/15/21
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)
** Please refer to page 3 for additional guidance on ECMO patients*

Oxygen saturation ≤ 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 ≤10 days OR ≤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

Tocilizumab x 1 dose within 24 hours of requiring NRB, HFNC, NIV, MV
If hospital length of stay is ≥ 7 days, consult Antimicrobial Stewardship/ID
(See Appendix 2 for exclusion criteria)

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

Consider MICU evaluation if O2 ≥ 5 L/min requirement or hemodynamic instability
(at YNHH see Appendix 4 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 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 & tocilizumab requests.

Report suspected adverse events related to therapeutics through RL solutions

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

YNHHS Initial Treatment Guidance for Hospitalized ADULTS with COVID-19

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Anticoagulation Dosing Guidelines (Non-Pregnant Patients)[¥]

D-dimer	Give Aspirin[#]?	BMI < 40 kg/m2	BMI ≥ 40 kg/m2
< 5 mg/L Prophylaxis	Yes	CrCl ≥ 30 mL/min • Enoxaparin 40mg sq daily CrCl < 30mL/min • Enoxaparin 30mg sq daily • Heparin 5000 units sq Q8-12H	CrCl ≥ 30 mL/min • Enoxaparin 40mg sq Q12H CrCl < 30mL/min • Enoxaparin 40mg sq Q24H • Heparin 7500 units sq Q8-12H
≥ 5 mg/L or Receiving convalescent plasma Intermediate Dose Prophylaxis	Yes	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* • DOAC CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H* • DOAC • Heparin 7500 units sq Q8-12H	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* • DOAC CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H* • DOAC • Heparin 7500 units sq Q8H
Confirmed VTE with diagnostic imaging TREATMENT[€]	No	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H • DOAC CrCl < 30mL/min • Enoxaparin 1mg/kg sq Q24H • DOAC • Therapeutic heparin	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H • DOAC CrCl < 30mL/min • 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/m2)	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 5a & 5b

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

YNHHS Treatment Guidance for Hospitalized ADULTS with COVID-19 requiring ECMO

Disclaimer: Remdesivir is the only FDA-approved agent to date. Updated 2/15/21
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Guidance for Patients with Confirmed COVID-19 and Refractory Respiratory Failure Requiring ECMO

Prior to cannulation
- Goals of care discussion
- Follow **YNHHS COVID-19 Severe Algorithm** for treatment and testing
- Evaluate for secondary causes of respiratory failure
- Order pre-ECMO cytokine panel

Evaluation / Management of Secondary Causes of Respiratory Failure
- Vigorous pulmonary toilette
- Infection – blood and sputum cultures
- Pulmonary embolism
- Heart failure – limited TTE

ECMO (24-48 hours)
- Order post-ECMO cytokine panel (after ~48 hours)
- Assess eligibility for clinical trials / expanded access protocols

ECMO (48 hours–2 weeks)
- Consider Allergy / Immunology and Infectious Diseases consultation
- Consider adjunctive therapeutic resources

ECMO (2-3 weeks)
- Revisit goals of care discussions if no clinical improvement after addressing potentially reversible processes

Potential Adjunctive Therapeutic Resources

- Consider convalescent plasma administration under EUA (**See Appendix 3**)
- Consult Allergy / Immunology to help target immune dysregulation
  - Evaluate for other available clinical trials of immunomodulators
- Cytokine adsorption via ECMO circuit

* Available options are subject to rapid change *

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

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
Drug: Remdesivir (RDV) Broad-spectrum nucleotide prodrug which inhibits RNA polymerase activity against pathogenic coronaviruses. **Tocilizumab (TCZ)** Monoclonal antibody which inhibits soluble and membrane-bound IL-6R <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. <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. 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	Inclusion	• Informed consent or assent (depending on age) • 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 • Requiring > 6L/min supplemental oxygen to maintain SpO2 > 93% • Agreement not to participate in another COVID-19 treatment trial while participating Ability for men and women of childbearing potential to adhere to contraception rules	Remdesivir: infusion reactions, elevated LFTs, kidney toxicity (dose-dependent and reversible), possible viral resistance Tocilizumab: infusion reactions, serious infections and opportunistic infections, GI perforations, hematological malignancies, demyelinating disorders, elevated LFTs	YNHH PI: Onyema Ogbuagu Lead CRC: Laurie Andrews laurie.andrews@yale.edu
	Exclusion	• If progression to death is imminent and inevitable within next 24hrs • Suspected active bacterial, fungal, viral, or other infection besides COVID-19 • Allergy to tocilizumab or other monoclonal antibodies or remdesivir • Active TB infection • Treatment with immunosuppressive/modulators in past 3 months • Participation in another drug clinical trial • eGFR < 30mL/min/1.73m2 • ALT or AST > 5x ULN • ANC < 1000/uL • PLT < 50,000/uL • Weight < 40kg • Pregnant/breastfeeding • Treatment with investigation drug with 5 half-lives or 30 days or randomization		

at time of hospital discharge of 10 days have not been completed).				
Convalescent plasma in COVID-19 patients Rationale: 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. Description: Randomized, blinded phase 2 study evaluating the safety and efficacy of convalescent plasma compared to placebo in hospitalized patients with COVID-19	Inclusion	• Patients ≥18 years of age • Hospitalized with COVID-19 with respiratory symptoms, cough, chest pain, shortness of breath, fever, or oxygen saturation ≤ 94%, or abnormal imaging • Hospitalized for less than 72 hours OR within day 3 to 7 days from first signs of illness • Laboratory confirmed COVID-19 • On supplemental oxygen, non-invasive ventilation or high-flow oxygen • 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.		Clinical Trial Currently only at YNHH (YSC and SRC) Contacts : YNHH : Mahalia.desruisseaux@yale.edu
	Exclusion	• Receipt of pooled immunoglobulin in past 30 days • Contraindication to transfusion or history of prior reactions to transfusion blood products • Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) • Volume overload secondary to congestive heart failure or renal failure • Intracranial bleed		
Drug: Tofacitinib Selective JAK1 and JAK3 inhibitor Rationale: 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 Description: 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.	Inclusion	• Hospitalized patients aged 18-65 with lab-confirmed SARS-CoV-2 • Evidence of pneumonia by radiographic imaging (chest x-ray or chest CT scan) AND Requiring ≥ 3L O2 OR ≥ 2L O2 and hsCRP > 70 mg/L • Provide informed consent • Willingness to conform to contraceptive guidance	URTI, viral infections, herpes simplex. Joint/muscle/ligament swelling/pain	YNHH PI: Hyung Chun hyung.chun@yale.edu Clinical Research Assistant: Danielle Peterson

	Exclusion	• Require mechanical ventilation or ECMO on day 1 at time of randomization
		• Current or history of VTE (DVT or PE)
		• Personal or first-degree family history of blood clotting disorders
		• Immunocompromised or taking immunosuppressive agents
		• Current malignancy or lymphoproliferative disorders requiring active treatment
		• Females of child bearing potential or pregnant/breastfeeding
		• Other medical/psychiatric conditions which the investigator determines as inappropriate for participation
		• Survival < 72hrs
		• Infection History
		  ○ Secondary bacterial pneumonia
		  ○ Active herpes zoster		

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		○ Known tuberculosis or inadequately treated tuberculosis ○ Known HBV, HCV, or HIV. • Prior/Concomitant Therapy ○ 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 ○ Within 48hrs prior to first dose: treatment with corticosteroids equivalent to prednisone 20mg/day or treatment with herbal supplements • Diagnostic Assessment ○ Severe hepatic impairment, defined as Child-Pugh class C. ○ Hgb <8 g/dL ○ WBC < 1000/mm3, absolute lymphocyte count < 500 cells/mm3, absolute neutrophil count <1000 cells/mm3 ○ ALT/AST > 5 x ULN ○ eGFR < 40mL/min/1.73m2 • Allergy to tofacitinib • Enrollment in another clinical trial to study COVID-19		
I-SPY COVID-19 **Drugs:** 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 <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	**Inclusion/ Exclusion**	**Inclusion Criteria** • 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 **Exclusion Criteria** • 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		YNHH PI: Jon Koff Jon.koff@yale.edu RC: Jacqueline Prinz Jacqueline.prinz@yale.edu

care plus remdesivir and dexamethasone. Each additional study arm is an intervention that is evaluated for safety and efficacy via rolling DSMB review.		• 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		

Investigation of IRAK4 Inhibition to Mitigate the Impact of COVID-19 in Severe SARS-CoV-2 (I-RAMIC)
 	
Rationale: 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.
 	
Description: 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.
	Inclusion/ Exclusion	**Inclusion Criteria**
		• 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):
		  ○ Ferritin
		  ○ Procalcitonin
		  ○ D-dimer
		  ○ Fibrinogen
		  ○ LDH
		  ○ PT/PTT
		
		Exclusion Criteria
		• 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
				YNHH PI: Hyung Chun
				hyung.chun@yale.edu
				
				Clinical Research Assistant: Danielle Peterson

		• 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:
		  ○ 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.
		• Participation in other clinical trials of investigational treatments for COVID-19
		• Known history of nephrolithiasis		

Drug: Ibudilast (MN-166) Rationale: 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	Inclusion	• 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 $\leq$ 92% on room air (RA), RR $\geq$ 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 $\geq$ 65, underlying serious heart disease, chronic lung disease, moderate to severe asthma, body mass index $\geq$ 40, or diabetes) C-reactive protein >35 mg/L	Ibudilast: Adverse drug reactions are related to GI upset (anorexia, abdominal pain, nausea, vomiting, diarrhea) Others include headache, elevated LFTs, decreased WBC	YNHH PI: Maor Sauler Lead CRC: Linda Koumpouras maor.sauler@yale.edu 862-668-6341

and severity of ARDS. Ibudilast is also a phosphodiesterase inhibitor, particularly PDE 3, 4, 10, and 11, and may reduce platelet aggregation. <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)	Exclusion	• 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	count, and transient ataxia.	

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 ≥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 ≥ 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: COVID-19 Convalescent Plasma (CP) Inclusion/Exclusion Criteria

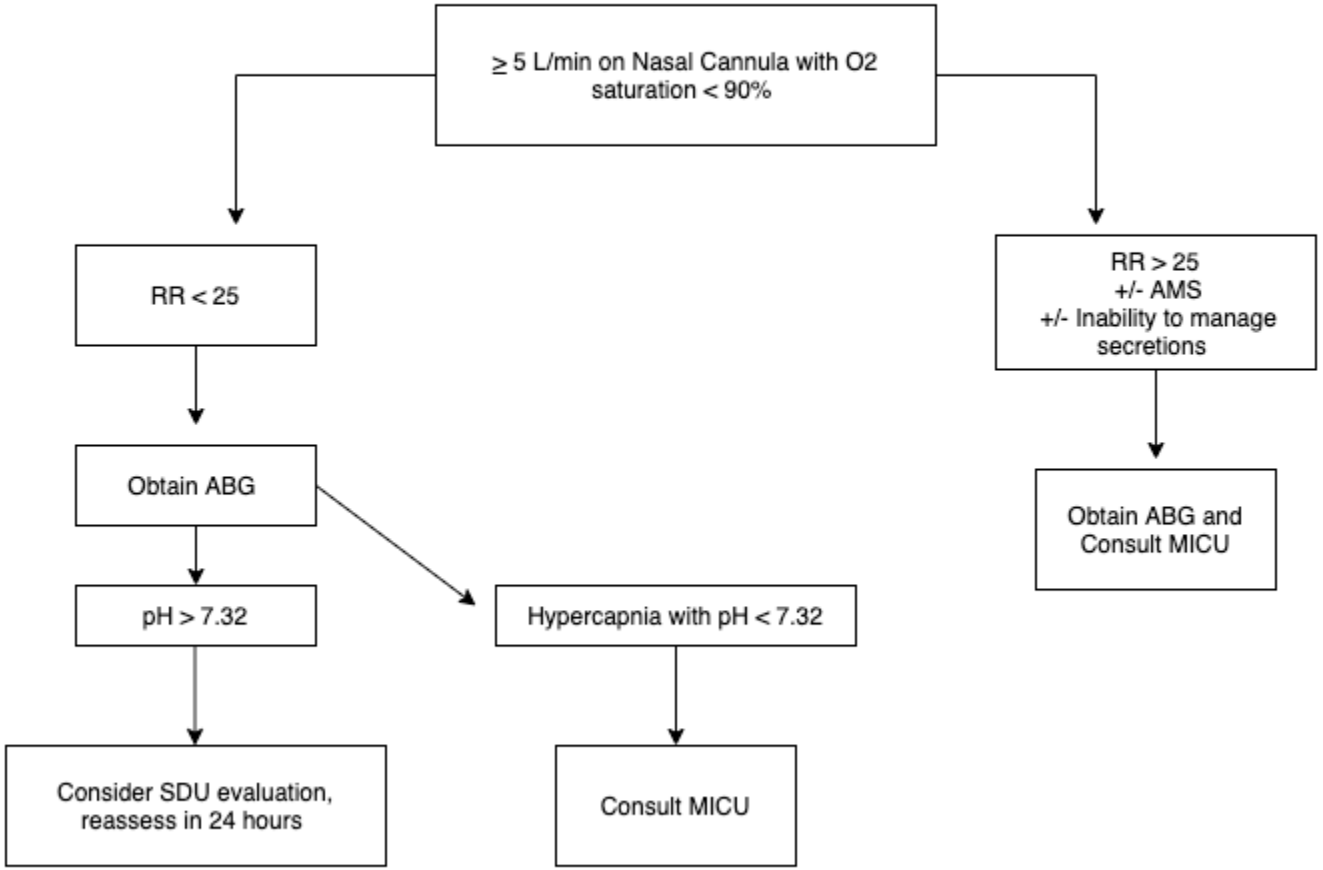
Convalescent Plasma is not stocked in any YNHHS hospital and can take up to 36 hours to obtain
Per the FDA EUA ONLY high titer product can be utilized which may not always be available

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 ≤ 3 days **AND** requires ≥ 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. Requiring > 6 L/min of oxygen supplementation or NRB, HFNC, NIV or MV
    c. History of anaphylaxis to blood products or history of IgA deficiency
    d. D-dimer > 10
    e. Evidence or suspicion of thrombosis
    f. Active bleed or high risk for bleeding
    g. Beyond 3 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[#] ?	BMI < 40 kg/m2	BMI ≥ 40 kg/m2
< 3.5 mg/L **Prophylaxis**	Yes	CrCl ≥ 30 mL/min • Enoxaparin 40mg sq daily CrCl < 30mL/min • Enoxaparin 30mg sq daily	CrCl ≥ 30 mL/min • Enoxaparin 40mg sq Q12H CrCl < 30mL/min • Enoxaparin 40mg sq Q24H
≥ 3.5 mg/L **or receiving convalescent plasma** **Intermediate Dose Prophylaxis**	Yes	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H*	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H*
≥ 7 mg/L **Confirmed VTE by diagnostic imaging** **TREATMENT**	No	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H CrCl < 30mL/min • Enoxaparin 1mg/kg sq Q24H	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H CrCl < 30mL/min • 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 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 >/= 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 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**
Remdesivir (1-8)	200mg IV once followed by 100mg IV daily for 5 days	• Viral RNA dependent RNA polymerase inhibitor	• *In-vitro* data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit	• Nausea, vomiting, • Elevated liver enzymes • Rectal bleeding	• 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	• Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression	• Can attenuate cytokine release in patients in patients with severe disease	• 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	• 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 (14-25)	8mg/kg IV x 1 dose (actual body weight; dose max 800 mg)	• Monoclonal antibody to IL6 receptor	• IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease • Prospective and retrospective data suggest possible benefit	• Headache • Elevated liver enzymes • Infusion reactions (e.g. flushing, chills)	• 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 x10^9/L
Available Therapy through Clinical Trial or Emergency Use Authorization (EUA) **(Subject to change as more data becomes available and based on medication availability)**					
Convalescent Plasma (26-31)	One ABO compatible unit	• Individual (not pooled) plasma from a recovered COVID19 patient	• Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis	• Transfusion reactions • Potential to increase hypercoagulability	• Each unit may contain variable titers of anti-SARS-CoV-2 antibodies with differing avidity • Cannot be used in patients with IgA deficiency due to risk of anaphylaxis • Use with intermediate dosing anticoagulation (see Appendix 5 above) • See Appendix 3
Therapy with limited data **(Current use is preferred to be given under clinical trials)**					
Baricitinib (32, 33)	N/A	• Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase, may inhibit viral entry via endocytosis	• May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors	• Risk of severe infections with use and possible increase of thrombosis	• Not available for off label use • No published data • FDA issued EUA of remdesivir and baricitinib but data of its safety and efficacy are not available.

Therapy with NO data for Hospitalized Patients (Current use is preferred to be given under clinical trials)					
Ivermectin(34)	N/A	• Inhibition of SARS CoV-2 viral replication	• In vitro data demonstrated potent inhibition of viral inhibition	• Pruritus, dermatological reaction, lymphadenitis, arthralgia, synovitis, fever	• **There is a lack of clinical data to support the use of ivermectin for the treatment of COVID-19** • Although *in-vitro* data demonstrated potent anti-SARS CoV-2 activity, further validation with *in vivo* models is required
Fluvoxamine (35, 36)	N/A	• σ-1 receptor agonist (SSRI)	• Potential immune modulation via σ-1 receptor (S1R) agonism	• Headache, insomnia, drowsiness, dizziness, nervousness, Nausea, diarrhea, xerostomia, anorexia, Ejaculatory disorder, weakness	• **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 in **non-hospitalized patients** found a lower likelihood of clinical deterioration with COVID-19 treated with fluvoxamine compared with placebo[35], 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.
Colchicine(37)	N/A	• Anti-gout agent	• Inhibition of PMN cell migration • Anti-inflammatory and anti-viral properties[36]	• Gastrointestinal side effects	• **The use of colchicine for the treatment of COVID-19 in hospitalized patients is not currently recommended by national or international guidelines** • The COLCORONA phase III trial to evaluate the efficacy and safety of colchicine for 30 days in **adult outpatients** diagnosed with COVID-19 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. [37]

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