YNHHS Initial Treatment Algorithm for Hospitalized ADULTS with Non–Severe* COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted – Algorithm last updated 5/27/20

Patient with **confirmed POSITIVE** SARS-CoV-2 by PCR

Assess all patients routinely for clinical trial eligibility (see Appendix 1)

*(If mechanically ventilated or on ECMO, proceed to Severe algorithm)

Oxygen saturation ≤ 94% on room air and requiring supplemental oxygen (**≤ 95%** if pregnant), or oxygen requirement above home baseline

YES

NO

SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING

Remdesivir x 5 days if hospital length of stay is ≤10 days

Use only when benefit may outweigh risk if eGFR <30 mL/min, hepatic dysfunction, or pregnancy (See Appendix 2 for exclusion criteria)

Remdesivir has not been FDA approved; remdesivir is authorized by the FDA under and Emergency Use Authorization (EUA)

If **≥ 3 Liter O2 requirement**
OR **≥ 2 Liter O2 requirement & hs-CRP >70**
Tocilizumab x 1 dose
(see Appendix 2 for exclusion criteria)

Consider MICU evaluation if > 4 Liter O2 requirement or hemodynamic instability
(at YNHH see Appendix 4 for suggested triage guidelines)

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

COVID-SPECIFIC TESTS

1) **Baseline & every 12 hours (for 5 days, then daily thereafter):** CRP, D-dimer
2) **Baseline & every 12 hours x3:** Troponin (continue longer if further testing clinically indicated)
3) **Baseline & every 24 hours (for 5 days*):** CBC with differential, BMP, LFTs, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
4) **Baseline & ICU transfer:** Cytokine panel
5) **Baseline and with acute kidney injury (AKI):** urinalysis and urine protein/albumin ratio
6) **Baseline EKG** (see Appendix 3 for QTc recommendations)
7) **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

See Page 3 of algorithm for multi-disciplinary management by sub-specialty recommendations

Report suspected adverse events related to therapeutics through RL solutions

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

YNHHS Initial Treatment Algorithm for Hospitalized ADULTS with Severe COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted - Algorithm last updated 5/27/20

Patient with **confirmed POSITIVE** SARS-CoV-2 by PCR

Assess all patients routinely for clinical trial eligibility (see Appendix 1)

Remdesivir x 5 days if hospital length of stay is ≤10 days

Use only when benefit may outweigh risk if eGFR <30 mL/min, hepatic dysfunction, or pregnancy (See Appendix 2 for exclusion criteria)

Remdesivir has not been FDA approved; remdesivir is authorized by the FDA under and Emergency Use Authorization (EUA)

If **≥ 3 Liter O2 requirement**
OR **≥ 2 Liter O2 requirement & hs-CRP >70**
Tocilizumab x 1 dose
(see Appendix 2 for exclusion criteria)

If worsening ARDS after 48 hours:

Consider methylprednisolone 40mg Q8H **for 72 hours.** Reassess for extended course or taper (up to 5-7 days total).
Steroids given at discretion of primary team

COVID-SPECIFIC TESTS

1) **Baseline & every 12 hours (for 5 days, then daily thereafter):** CRP, D-dimer
2) **Baseline & every 12 hours x3:** Troponin (continue longer if further testing clinically indicated)
3) **Baseline & every 24 hours*:** CBC with differential, BMP, LFTs, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
4) **On ICU admission:** Cytokine panel
5) **Baseline and with acute kidney injury (AKI):** urinalysis and urine protein/albumin ratio
6) **Baseline EKG** (see Appendix 3 for QTc recommendations)
7) **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

If patient on ECMO or planned for ECMO, also see **ECMO** algorithm

YNHH: ID consult is not mandatory for remdesivir or tocilizumab. Make requests for tocilizumab and remdesivir through the non-formulary / restricted medication consult to pharmacy.
BH, GH, LMH, or WH: consult ID for remdesivir and tocilizumab requests

Report suspected adverse events related to therapeutics through RL solutions

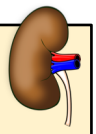
See Page 3 of algorithm for multi-disciplinary management by sub-specialty recommendations

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

YNHHS Initial Treatment Algorithm for Hospitalized ADULTS with COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted - Algorithm last updated 5/27/20

Nephrology:



-If acute kidney injury, check urinalysis and baseline urine protein/albumin.

-If **≥ 1 gram of protein,** consider renal input

Hematologic:

-**If D-dimer <5 mg/L**: All patients should receive **standard prophylactic anticoagulation and aspirin 81mg daily** unless contraindicated★

-**If D-dimer ≥5mg/L or receiving convalescent plasma:** use **weight-based intermediate prophylactic anticoagulation and aspirin 81mg daily** unless contraindicated★

-If **confirmed VTE or high clinical suspicion**, start **therapeutic dose anticoagulation and aspirin 81mg daily** unless contraindicated★

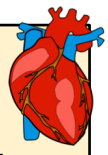
-If ferritin >100,000 or D-dimer >10mg/L, consider Hematology consult at discretion of primary team

(★see Appendix 5 for anticoagulation dosing recommendations)

Aspirin 81mg PO daily

- Relative contraindications: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder
- Discontinue at discharge

Cardiac:



-Monitor electrolytes: **Replete Mg >2, K >4**

-Baseline **EKG and monitor telemetry** closely for QTc Prolongation (Appendix 2 for recommendations)

-Caution combining QTc prolonging medications

-If significantly elevated troponin or EKG abnormalities and/or hemodynamic instability, consider POCUS for LV function assessment and cardiology consult

Obstetrics:

Treatment Protocol is similar.
Alternative cut-offs for:
-Treatment administration with oxygen saturation of ≤ 95%.
-D-dimer cutoff for anticoagulation (see Appendix 5b)

Remdesivir is available to pregnant patients under Expanded Access / Compassionate Use requests. Request only if potential benefits outweigh risks.

***Immunosuppressed hosts** include: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone ≥20mg daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, vasculitis, and pregnancy

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

YNHHS Algorithm for Hospitalized ADULTS with COVID-19 requiring ECMO

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted – Algorithm last updated 5/27/20

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

- Convalescent plasma administration if eligible
- Consult Allergy / Immunology to help target immune dysregulation
  - Sarilumab trial if eligible (current trial excludes patients who received an IL-6 antagonist in the prior 30 days)
  - Possible repeat tocilizumab dosing
- Cytokine adsorption via ECMO circuit

* Available options are subject to rapid change *

Algorithm 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: Sarilumab Monoclonal antibody to IL6 receptor Rationale: IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease Description: Phase 2/3, Randomized, Double-Blind, Placebo Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19	Inclusion	• Aged ≥ 18 years • Evidence of pneumonia and have one of the following disease categories: severe disease, multi-system organ dysfunction or critical disease Laboratory-confirmed SARS-CoV-2 infection	Elevated liver enzymes Leukopenia Infusion reactions (e.g. flushing, chills)	PI: Geoffrey Chupp Contact : Geoffrey.Chupp@yale.edu
	Key Exclusion	• Low likelihood of survival after 48 hours from screening • Presence of neutropenia less than 2000/mm^3 • AST or ALT greater than 5 X ULN • Platelets < 50,000/mm^3 prior immunosuppressive therapies • Use of chronic oral corticosteroids for non-COVID-19 related condition • Patients who have received IL-6 receptor antagonist within 30 days of study enrollment • Participation in any other clinical trial of an experimental treatment for COVID-19 • Known or suspected history of tuberculosis • Suspected or known active systemic bacterial or fungal infection		

Expanded access program for use of **convalescent plasma** in COVID-19 patients	Inclusion	• Aged ≥ 18 years
		• Confirmed positive SARS-CoV-2 infection by PCR
		• Severe or Life-threatening disease by the following definitions
		• Severe disease
		  ○ Requiring supplemental oxygen with one or more of the following:
		  ▪ Non-rebreather
		  ▪ High-flow nasal cannula
		  ▪ Pulmonary infiltrates with ≥ 3 L via NC with rapid progression
		  ▪ Mechanical ventilation
		• Life-threatening disease
		  ○ Refractory respiratory failure, or
		  ○ Septic shock, or
		  ○ Multi-organ dysfunction
				Contacts :
				YNHH :
				Mahalia.desruisseaux@yale.edu
				BH:
				Tina.McCurry@bpthosp.org
				GH:
				James.Sabetta@greenwichhospital.org
				LMH/WH:
				Christopher.Song@lmhosp.org

	Relative Exclusion	• ≥ 10 days since first positive SARS-CoV-2 PCR • Confirmed or high suspicion for bacterial or fungal infection • D-dimer ≥ 5 mg/L or evidence of/suspicion for thrombosis • Recent bleeding or high risk for bleeding • Known severe IgA deficiency		

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 they should 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 and Tocilizumab 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% FiO_2; 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: Care Pathways for Mitigation of Drug-Induced Malignant Arrhythmias in COVID-19 Patients

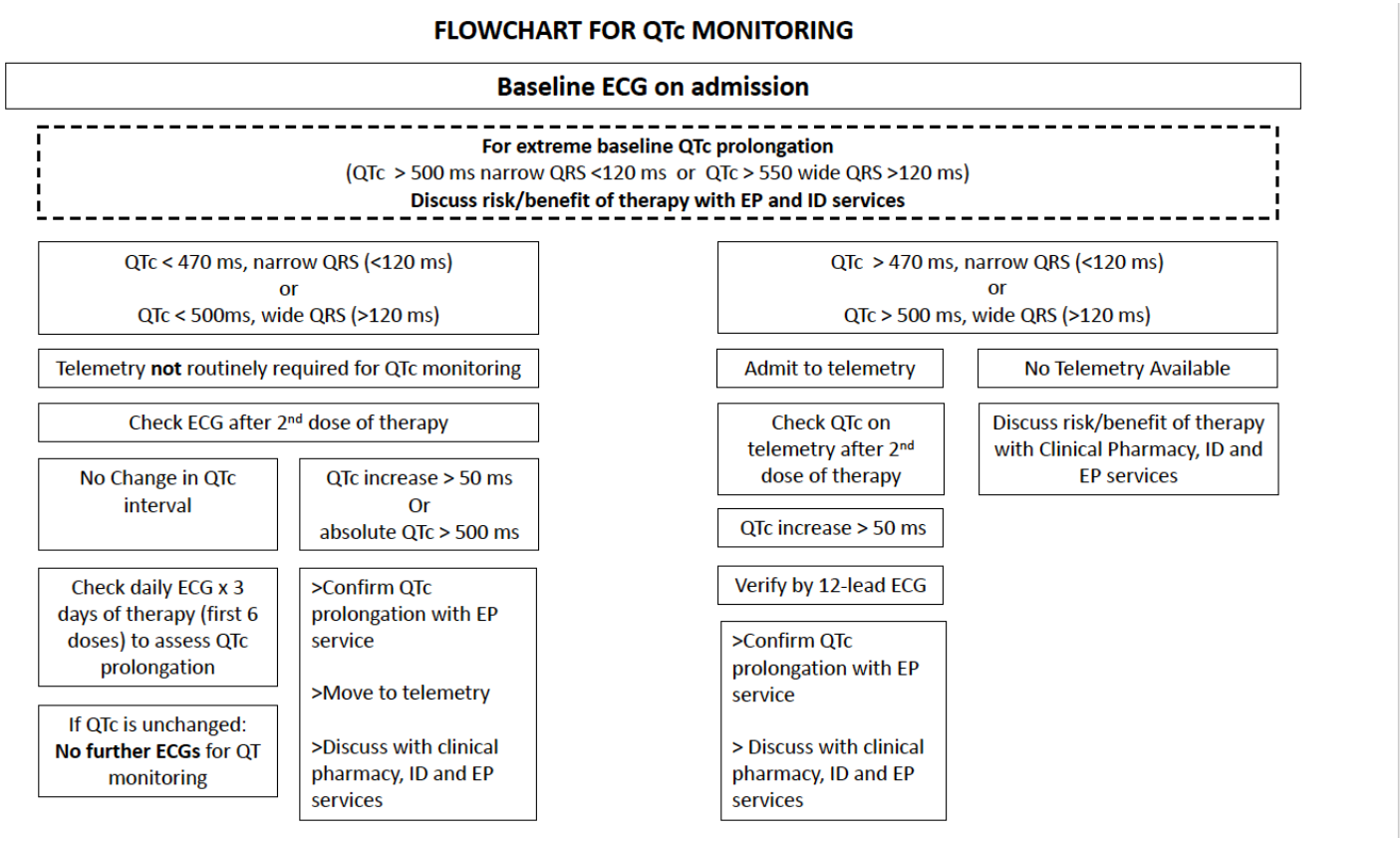
Recommendations:

All COVID-19 patients should have the following:

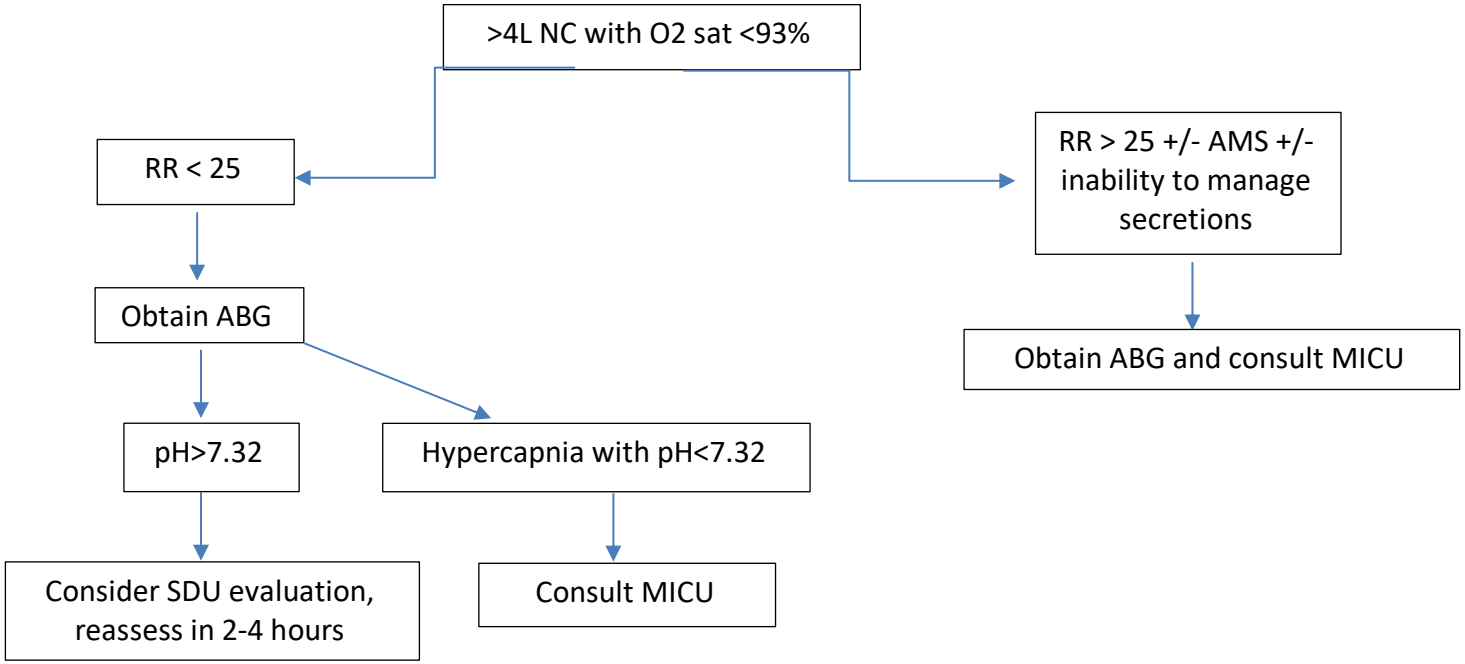
- When ordering an EKG for a COVID 19 patient to monitor their QTc, select the diagnosis “COVID 19” to alert cardiology to expedite the formal reading of the EKG.
- Daily monitoring of electrolytes; maintain K > 4 and Mg > 2
- All unnecessary QT prolonging drugs should be avoided or switched to alternatives whenever possible.

Recommendations:

A flowchart for the monitoring of potential malignant arrhythmias in these patients is shown below.



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



Appendix 5a: Anticoagulation Dosing Guidelines (Non-Pregnant Patients)[¥]

Administer aspirin 81mg PO daily to all patients unless contraindicated.[◊] Discontinue aspirin at discharge.

D-dimer	BMI < 40 kg/m2	BMI ≥ 40 kg/m2
< 5 mg/L Prophylaxis	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	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, high clinical suspicion, or clotting of dialysis lines/tubing TREATMENT[€]	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 Dosing

DOAC	D-dimer ≥ 5 mg/L Intermediate Dose Prophylaxis	Confirmed VTE treatment, high clinical suspicion or clotting of dialysis lines/tubing
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)
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

[¥]Enoxaparin is the preferred form of anticoagulation

[◊]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, including duration and extended prophylaxis for discharge

Appendix 5b: Anticoagulation Dosing Guidelines (Pregnant Patients)

Administer aspirin 81mg PO daily to all patients unless contraindicated.◊ Discontinue aspirin at discharge.

D-dimer	BMI < 40 kg/m2	BMI ≥ 40 kg/m2
< 3.5 mg/L **Prophylaxis**	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**	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 or high clinical suspicion** **TREATMENT**	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

◊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 6

Possible medications for COVID-19 (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 (1-7)	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 authorized (not approved) by the FDA through an Emergency Use Authorization (EUA). Availability under the EUA is limited. • Available for pregnant patients and patients on ECMO under Expanded Access; request only if benefits outweigh risks
Tocilizumab (8-14)	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 • Retrospective data suggest possible benefit (clinical trials ongoing)	• 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
Medications which may be available through Clinical Trials or Expanded Access **(Subject to change as more data becomes available and based on medication availability)**					
Convalescent Plasma (15-19)	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 •	• Available through expanded access, not a trial • 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) .
Sarilumab (20-22)	Clinical Trial dosing	• Monoclonal antibody to IL6 receptor	IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease	• Elevated liver enzymes • Leukopenia Infusion reactions (e.g. flushing, chills)	• Available through clinical trial only at this time

Medications NOT currently recommended as first line for COVID-19

(Can be considered in certain cases after discussion with Infectious Diseases and Pharmacy)

Drug	Dose	Mechanism	Rationale for possible efficacy	Rationale for NOT including as first line agent
Hydroxy-chloroquine (HCQ) (7, 23-37)	400mg PO q12h x 24h, then 200mg q12h x 4 days for a 5 day total duration	• Prevents acidification of endosomes interrupting cellular functions and replication • Prevents viral entry via ACE2 binding • Reduction of viral infectivity • Immunomodulator	• In-vitro data shows potent SARS-COV-2 inhibition and early clinical data shows possible benefit • HCQ was found more potent than chloroquine in inhibiting SARS-CoV-2 in vitro	• Available data from clinical trials does not demonstrate benefit, and some studies suggest risk. Risks outweigh benefits given theoretic risk for cardiac arrhythmia.
Lopinavir/ Ritonavir (38-41)	N/A	• Viral protease inhibitor	• In-vitro data reveals potent SARS-COV-2 inhibition	• Limited availability, poor tolerability (such as GI side effects) and recent data demonstrated questionable clinical efficacy
Atazanavir (42)	N/A	• Viral protease inhibitor	• More potent binding to the virus compared to other protease inhibitors *in vitro* (lower than lopinavir) • Drug more widely available than other PI's including lopinavir/ritonavir and better tolerated	• Mild indirect hyperbilirubinemia is common and not indicative of hepatic dysfunction • CYP enzyme inhibitor (3A4, 2C8) monitor/discuss with pharmacy potential for drug-drug interactions • For patients with NG/OG/NJ open capsules for enteral administration • Atazanavir needs an acidic environment for absorption and therefore ***antacids, H2 blockers, proton pump inhibitors (PPIs)*** **should be avoided**. If these agents must be given the administration should be separated as below: o Atazanavir should be given 2 hours before or 1 hour after antacids o Atazanavir should be given at the same time as the H2 blocker or the atazanavir should be given 10 hours after or 2 hours before the H2 blocker • For PPIs avoid concomitant use

Azithromycin (43)	500 mg x 1, followed by 250 mg q24h x 4 days	• Not well defined; possible immunomodulator	• In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load	• Very limited data on use of azithromycin alone or in combination with other agents ○ Gautret, et al. study is limited by small sample size (only 6 patients received HCQ & azithromycin combination) and those patients had lower viral loads than other included patients • Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation
Darunavir/ Cobicistat (44)	N/A	• Viral protease inhibitor	• In-vitro data shows SARS-COV-2 inhibition	• Decreased binding to viral protease compared to atazanavir. No clinical data at this time
Ribavirin (45, 46)	N/A	• Viral RNA polymerase inhibitor and inhibition of elongation of RNA fragments	• *In vitro* data for use in SARS-CoV and MERS-CoV indicates possible activity	• Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use • Typically used with interferon • Studied in patients with other coronaviruses with mixed results
Oseltamivir (47)	N/A	• Inhibits influenza virus neuraminidase blocking viral release	• Activity against influenza virus	• No current data to support use of this drug. • Additionally, **SARS-CoV-2 does not use neuraminidase in the replication cycle** so mechanistically there would be no benefit
Nitazoxanide (48)	N/A	• Augments host antiviral response	• *In-vitro* data reveals SARS-COV-2 inhibition	• No clinical data available

IMMUNOMODULATING AGENTS				
Interferon-beta (39-41, 49)	N/A	• Immunomodulator	• Possible activity against SARS-CoV and MERS-CoV • Typically used in combination with ribavirin	• Limited data with SARS-CoV-2, toxicity risk outweighs benefit of use. Have been studied for patients with other coronaviruses with mixed results • Not interferon-alpha or interferon-gamma

Corticosteroids (50-54)	If indicated per protocol: Methyl-prednisolone 40mg q8hr IV for three days, then re-assess	• Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression	• May be helpful in attenuating cytokine release in patients with severe disease	• Lack of effectiveness and potential harm shown in literature specifically inhibition of viral clearance in severe influenza and SARS [31-34], though possible benefit with critically ill COVID19 patients [35] • May be considered for use by critical care team for salvage therapy • ***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***
Intravenous immunoglobulin (IVIG) (55, 56)	N/A	• Neutralizing antibodies against the virus	• May have both antiviral and immunomodulatory effects • A recent observational study reported clinical and radiographic improvement in ***3 patients*** who received high dose IVIG at time of respiratory distress	• Drug is on ***critical national shortage*** and has an unclear role as current preparations will not contain antibodies against SARS-CoV-2 at this time
Baricitinib (57, 58)	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	• Not available for off label use • No clinical data available • Risk of severe infections with use
Zinc (59, 60)	N/A	• Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as RNA-dependent RNA polymerase. Chloroquine has been demonstrated to be a zinc ionophore. All data is based on in vitro studies only.	• Increasing intracellular zinc concentrations may inhibit RNA synthesis	• No clinical data is available to demonstrate efficacy in vivo. • No in vitro studies have evaluated the effect of zinc on SARS-CoV-2 replication, or hydroxychloroquine as a zinc ionophore

Ascorbic acid & Thiamine (61-64)	N/A	• Unclear; ?role in septic shock/ARDs	• ? benefit in septic shock/ARDs	• No published peer reviewed studies in the medical literature were found to support the usage of these vitamins for COVID-19. There are ongoing clinical trials assessing possible benefit. • Two recently published open-label studies evaluating the use of vitamin C alone and in combination in other types of infections, associated with septic shock and acute respiratory distress syndrome (ARDS) showed no clear evidence of benefit. It cannot be concluded that intravenous vitamin C or thiamine is an effective treatment of ARDS (resulting from COVID-19, or otherwise).

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