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 4/27/20

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

Assess all patients routinely for clinical trial eligibility (see Appendix 6)

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

A-Presence of :

Oxygen saturation ≤ 93% on room air OR *on chronic O_2 supplementation (if O2>93% see box B)*

YES → **START TREATMENT (see treatment below)**

NO → SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING

If **Oxygen saturation ≤ 93%** on room air
* For pregnant women , O2 sat ≤95%

B-Presence of:

1) Fever and/or **signs & symptoms of respiratory disease** (e.g. cough, dyspnea)

OR

2) Chest X-Ray showing lung opacities

YES → **Does patient have:**

Age ≥ 60 **OR**
BMI ≥ 30 **OR**
Diabetes (HgbA1c ≥ 8.0) **OR**
Chronic heart disease/HTN **OR**
Chronic lung disease **OR**
Immunosuppressed*

NO → SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING

YES → **START TREATMENT**

TREATMENT

Start hydroxychloroquine x 5 days

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

Consider MICU evaluation if > 4 Liter O2 requirement or hemodynamic instability
(at YNHH see Appendix 2 for suggested triage guidelines)

YNHH: ID consult is not mandatory; consider ID input if immunosuppressed* or clinically decompensating
BH, GH, LMH, or WH: consult ID

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

Report suspected adverse events related to therapeutics through RL solutions

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, CMP, 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,** and if not on telemetry**, daily EKG x 3.** (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**

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 4/27/20

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

Assess all patients routinely for clinical trial eligibility (see Appendix 6)

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

TREATMENT
Start Hydroxychloroquine x 5 days

YNHH: consider ID input as needed
BH, GH, LMH, or WH: consult ID

Consider **tocilizumab x 1 dose**
(see Appendix 1 for exclusion criteria)
in combination with hydroxychloroquine

If progression in 48 hours (worsening respiratory/clinical status or worsening inflammatory markers):

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

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

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, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
4) **Baseline and with acute kidney injury (AKI):** urinalysis and urine protein/albumin ratio
5) **On ICU admission:** Cytokine panel
6) **Baseline EKG,** and telemetry QTc monitoring. EKG for clinical change (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**

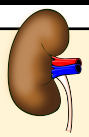
See Page 3 of algorithm for multi-disciplinary management by sub-specialty recommendations

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 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 4/27/20



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** unless contraindicated★

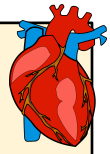
-**If D-dimer ≥5mg/L:** use **weight-based intermediate prophylactic anticoagulation** unless contraindicated★

-If **confirmed VTE or high clinical suspicion**, start **therapeutic dose anticoagulation** unless contraindicated★

-If sudden and unexplained change in O2 OR **new asymmetrical upper or lower extremity edema,** consider venous U/S of affected extremity

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

(★see Appendix 4 for dosing recommendations)



Cardiac:

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

-Baseline **EKG and monitor telemetry** closely for QTc Prolongation (Appendix 3 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 4b)

***Immunosuppression** includes following: 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

YNHHS Algorithm for Hospitalized ADULTS with SEVERE 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 4/27/20

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

Prior to cannulation
- Goals of care discussion
- Follow YNHH 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)
- Repeat SARS-CoV-2 PCR testing on endotracheal aspirate immediately after cannulation
- 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

Target virus if endotracheal SARS-CoV-2 PCR is positive
- Remdesivir compassionate use if eligible (Current Remdesivir trial excludes patients on ECMO)
- Convalescent serum administration if eligible

- and / or -

Target cytokines if immune dysregulation is present
- Consult Allergy / Immunology
  - Possible repeat Tocilizumab dosing
  - Sarilumab trial if eligible (Current trial excludes patients who received an IL-6 antagonist in the prior 30 days)
- 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: 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, advanc liver cancer

d. **Neurologic**: Severe dementia leading to dependence in multiple ADLs; Rapidly progressive or end-stage neuromuscular disease

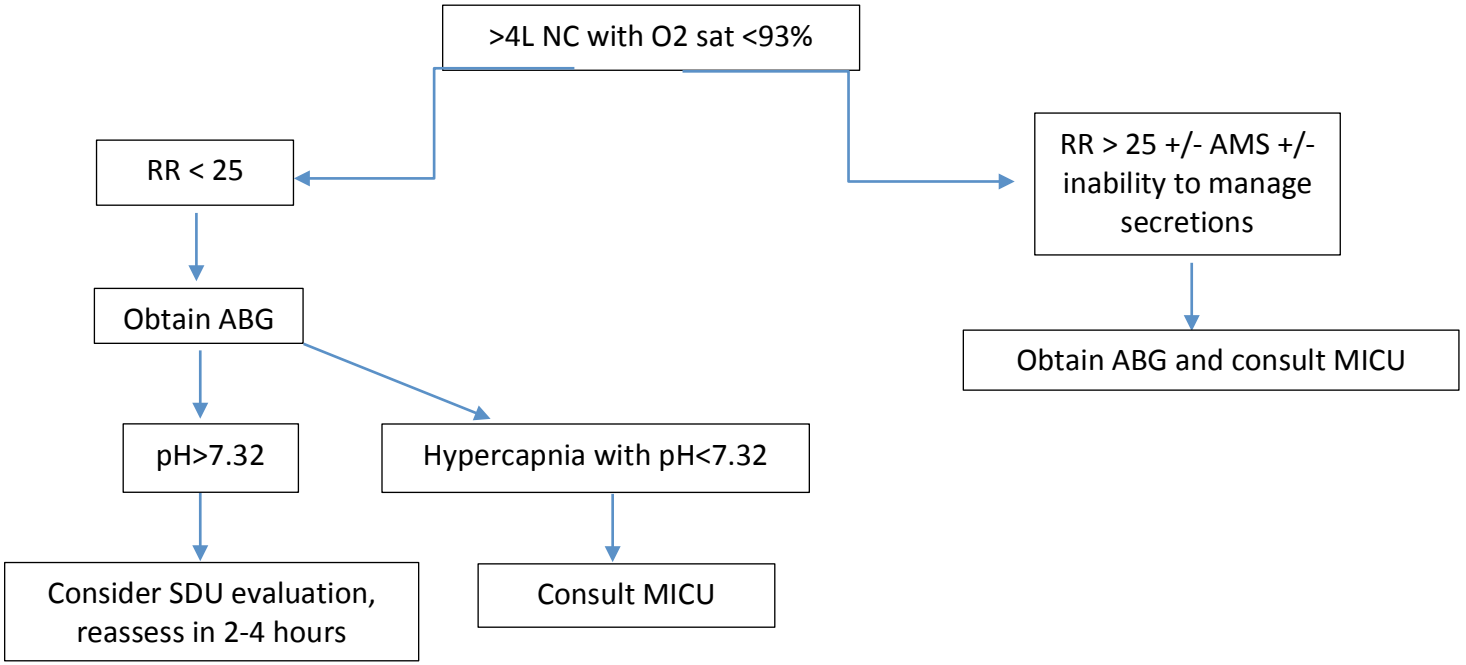
e. **Oncologic**: Advanced malignancy or high-grade primary brain tumors receiving only palliative treatment with estimated 3 or fewer month prognosis.

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



Appendix 3: Care Pathways for Mitigation of Drug-Induced Malignant Arrhythmias in COVID-19 Patients

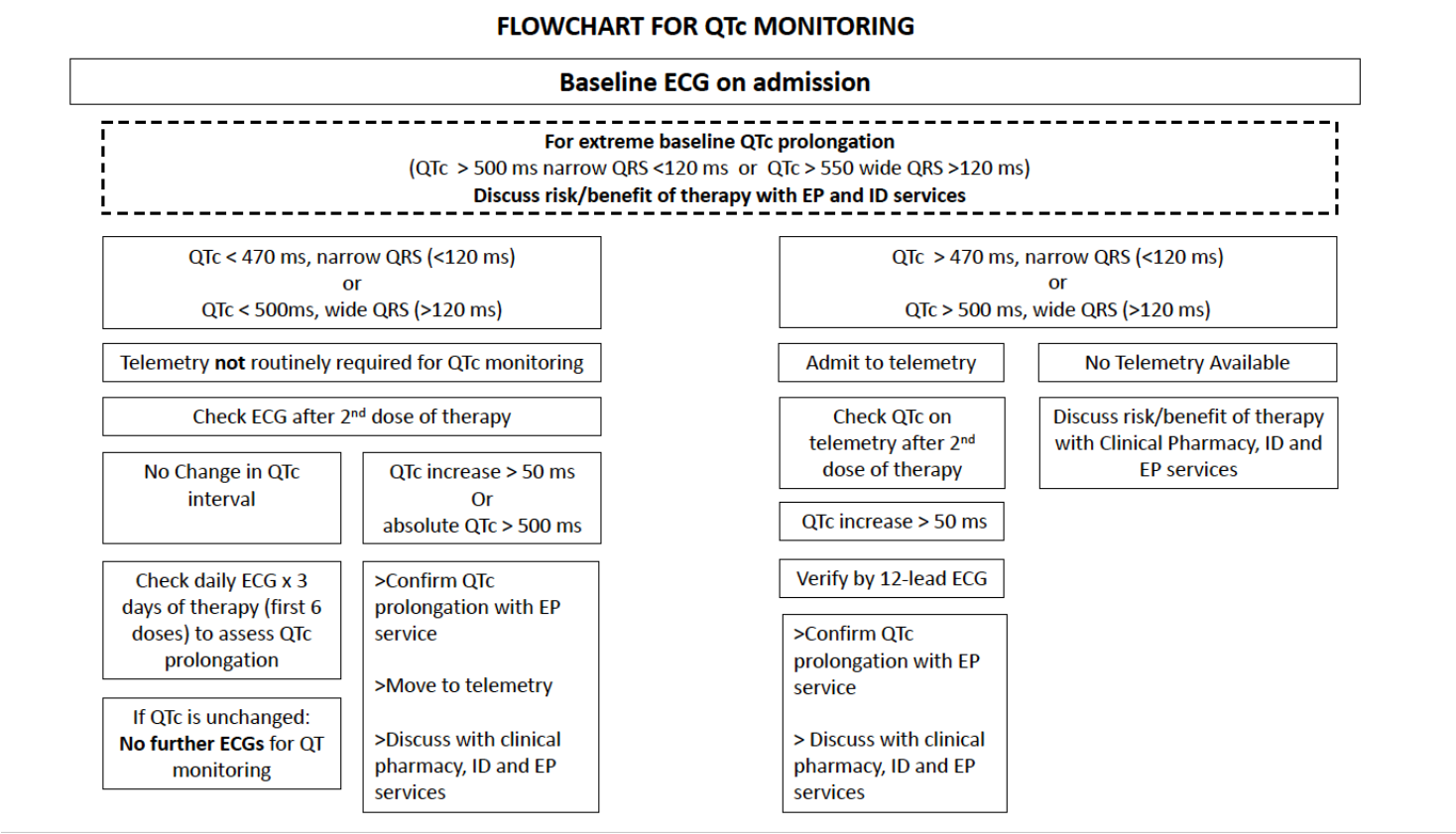
Recommendations:

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 readin 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 4a: Anticoagulation Dosing Guidelines (Non-Pregnant Patients)[¥]

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 **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

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

[¥]Enoxaparin is the preferred form of anticoagulation

[€]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 4b: Anticoagulation Dosing Guidelines (Pregnant Patients)

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 **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-PATRUM dosing should be PRE-PREGNANCY weight

*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 5

Currently recommended 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**
Hydroxy-chloroquine (HCQ)[1-9,48-52]	400mg PO q12h x 24h followed by 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	• QTc prolongation • Rash • Retinopathy is rare **(Baseline eye exam is not required for use for COVID-19**)	• There is a theoretical potential for an increase in hydroxychloroquine levels when used with atazanavir therefore ***monitor for possible QTc prolongation*** • For patients with NG/OG/NT hydroxychloroquine can be crushed for enteral administration
IMMUNOMODULATING AGENTS					
Tocilizumab[10-13]	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 **(Subject to change as more data becomes available and based on medication availability)**					
Remdesivir[14-17]	***Clinical Trial dosing***	• 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	• As of 3/22/20, remdesivir is available through clinical trials • Compassionate use program is available to pregnant patients and those < 18 years of age • Gilead will open an expanded access program

IMMUNOMODULATING AGENTS					
Sarilumab[18-20]	***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**
Lopinavir/ Ritonavir[8,21]	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[22] **NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir /ritonavir data**[19]	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[23]	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[24]	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[25-27]	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[28]	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[29]	N/A	• Augments host antiviral response	• *In-vitro* data reveals SARS-COV-2 inhibition	• No clinical data available

IMMUNOMODULATING AGENTS				
Interferon-beta[30-32]	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[33-37]	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)[38-39]	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 [40-41]	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[42,43]	N/A	• Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as	• 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

		RNA-dependent RNA polymerase. Chloroquine has been demonstrated to be a zinc ionophore. All data is based on in vitro studies only.		
Ascorbic acid & Thiamine[44-47]	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).

References:

1) Vincent MJ, Bergeron E, Benjannet S et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005; 2:69. (PubMed 16115318) (DOI 10.1186/1743-422X-2-69).
2) Olofsson S, et al. Avian influenza and sialic acid receptors: more than meets the eye? Lancet Infect Dis. 2005 Mar;5(3):184-8.
3) Yang ZY et al. pH-dependent entry of severe acute respiratory syndrome coronavirus is mediated by the spike glycoprotein and enhanced by dendritic cell transfer through DC-SIGN.J Virol. 2004 Jun;78(11):5642-50.
4) Savarino A, et al. Anti-HIV Effects of Chloroquine: Inhibition of Viral Particle Glycosylation and Synergism With Protease Inhibitors. J Acquir Immune Defic Syndr. 2004 Mar 1;35(3):223-32.
5) Klumperman J, et al. Coronavirus M proteins accumulate in the Golgi complex beyond the site of virion budding. J Virol. 1994 Oct;68(10):6523-34.
6) Schrezenmeier E and Dorner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatol. 2020 Mar;16(3):155-166. doi: 10.1038/s41584-020-037 Epub 2020 Feb 7.
7) Zhonghua J, et al. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. *CMAPH*. 2020 Feb;43(0):E019. DOI: 10.3760/cma.j.issn.1001-0939.2020.0019.
8) Yao X, Ye F, Zhang M et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syn-drome Coronavirus 2 (SARS-CoV- Clin Infect Dis. 2020; In Press. (PubMed 32150618) (DOI 10.1093/cid/ciaa237)
9) Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, and Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Doi.org/10.1101/2020.03.22.20040758
10) Brudno JN & Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. Blood Rev. 2019 Mar;34:45-55. doi: 10.1016/j.blre.2018.11.002. Epub 2018 Nov 14.
11) Rubin DB, et al. Neurological toxicities associated with chimeric antigen receptor T-cell therapy. Brain. 2019 May 1;142(5):1334-1348. doi: 10.1093/brain/awz053.
12) Anecdotal reports from Italy; Chinese National Health Commission Clinical Guideline, March 3, 2020. http://busan.china-consulate.org/chn/zt/4/P020200310548447287942.pdf
13) Xiaoling Xu, et al. Effective treatment of Severe COVID-19 Patients with Tocilizumab. http://chinaxiv.org/abs/202003.00026. (pre-print not peer reviewed)
14) Holshue ML, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med. 2020 Mar 5;382(10):929-936.
15) Wang M, Cao R, Zhang L et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020; 30:269-271. (PubMed 32020029) (DOI 10.1038/s41422-020-0282-0)
16) Clinical trials.gov (Identifier NCT04292899 and NCT04292730)
17) Grein, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med. 2020 Apr 10 doi: 10.1056/NEJMoa2007016. [Epub ahead of print]

18) Teachey DT, Rheingold SR, Maude SL, Zugmaier G, Barrett DM, Seif AE, et al. Cytokine release syndrome after blinatumomab treatment related to abnormal macrophage activation and ameliorated with cytokine-directed therapy. Blood 2013; 121(26):5154-7.
19) Tomonori Ishii ea. 2019. Pharmacodynamic effect and safety of single-dose sarilumab SC or tocilizumab IV or SC in patients with rheumatoid arthritis. Annual Meeting of the American College of Clinical Pharmacology. Bethesda, MD, USA.
20) Clinical Study Protocol 6R88-COV-2040 Original Regeneron Pharmaceuticals, Inc. Page 78
21) Cao B, Wang Y, Wen D et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020; (PubMed 32187464) (DOI 10.1056/NEJMoa2001282)
22) Yu-Chuan et al, Potential therapeutic agents for COVID-19 based on the analysis of protease and RNA polymerase docking, doi:10.20944/preprints202002.0242.v1 (not peer reviewed).
23) Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimi-crob Agnts. 2020; In Press. (DOI 10.1016/jantimicag.2020.105949)
24) Clinicaltrials.gov (Identifier NCT04252274)
25) Gross AE, et al. Oral Ribavirin for the Treatment of Noninfluenza Respiratory Viral Infections: A Systematic Review. Ann Pharmacother. 2015 Oct;49(10):1125-35.
26) Arabi YM, Alothman A, Balkhy HH et al. Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial. Trials. 2018; 19:81. (PubMed 29382391) (DOI 10.1186/s13063-017-2427-0)
27) Mo Y, Fisher D. A review of treatment modalities for Middle East Respiratory Syndrome. J Antimicrob Chemother. 2016 Dec;71(12):3340-3350.
28) Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507–513. PMID: 32007
DOI: 10.1016/S0140-6736(20)30211-7.
29) Gamino- Arroyo AE, et al. Efficacy and Safety of Nitazoxanide in Addition to Standard of Care for the Treatment of Severe Acute Respiratory Illness. Clin Infect Dis. 2019 Nov 13;69(11):1903-1911.
30) Cinatl J et al. Treatment of SARS with Human Interferons. *Lancet*. 2003; 362(9380): 293-294.
31) Chan JF-W, Yao Y, Yeung M-L, et al. Treatment With Lopinavir/Ritonavir or Interferon-β1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset. *The Journal of infectious diseases.* 2015;212(12):1904-1913.
32) Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature communications.* 2020;11(1):222.
33) Lee N, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. J Clin Virol. 2004 Dec;31(4):304-9.
34) Stockman LJ, et al. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep;3(9):e343.
35) Arabi et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome.Am J Respir Crit Care Med. 2018 Mar 15;197(6):757-767. doi: 10.1164/rccm.201706-1172OC.
36) WHO. COVID-19 Guidelines, 2020 .https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance
37) Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar
doi: 10.1001/jamainternmed.2020.0994. PMID: 32167524.
38) Hu H, et al. Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. Eur Heart J. 2020 Mar 16. pii: ehaa190. doi: 10.1093/eurheartj/ehaa190.
39) Cao et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. *Open Forum Infectious Diseases*, ofaa102, https://doi.org/10.1093/ofid/ofaa102
40) Richardson P, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet. 2020 Feb 15;395(10223):e30-e31.
41) Stebbing J, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis. 2020 Feb 27. pii: S1473-3099(20)30132-8.
42) te Velthuis AJW, van den Worm, SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn^{2+} Inhibits Coronavirus and Arterivirus RNA Polymerase Activity *In Vitro* and Zinc Ionophores Block the Replication of These Viruses in Cell Culture. PLoS ONE. 2010; 6(11): 1-10.
43) Zue J, Moyer A, Peng B, Wu J, Hannafon BN, et al. Chloroquine is a Zinc Ionophore. PLoS ONE; 9(10): 1-6.
44) Fowler AA, Truwit JD, Hite RD, et al. 2019. Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients With Sepsis and Severe Acute Respiratory Failure: T CITRIS-ALI Randomized Clinical Trial. *JAMA* 322(13):1261-1270.
45) Fujii T, Luethi N, Young PJ, et al. 2020. Effect of Vitamin C, Hydrocortisone, and Thiamine vs Hydrocortisone Alone on Time Alive and Free of Vasopressor Support Among Patients With Septic Shock: The VITAMINS Randomized Clinical Trial. *JAMA* doi: 10.1001/jama.2019.22176.
46) Matthay MA, Aldrich JM, Gotts JE 2020. Treatment for severe acute respiratory distress syndrome from COVID-19. *Lancet Respir Med* doi: 10.1016/S2213-2600(20)30127-2.
47) Marik PA. EVMS Critical Care COVID-19 Management Protocol. https://www.evms.edu/media/evms_public/departments/internal_medicine/EVMS_Critical_Care_COVID-19_Protocol.pdf
48) Magagnoli et al. Pre-Print (not peer reviewed). Outcomes of hydroxychloroquine usage in United States veterans hospitalized with COVID 19. https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v2.
49) Borba et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, phase IIb clinical trial (CloroCovid-19 Study). Preprint (not peer reviewed). https://www.medrxiv.org/content/10.1101/2020.04.07.20056424v1.full.pdf
50) Tang et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. Preprint (not peer reviewed). https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1
51) Chen et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Preprint (not peer reviewed). https://www.medrxiv.org/content/10.1101/2020.03.22.20040758
52) Mahevas et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a tai trial. Preprint (not peer reviewed). https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1.full.pdf

Appendix 6: 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** Viral RNA dependent RNA polymerase inhibitor Rationale: In-vitro data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit Description: A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19	Mild / Moderate Disease	Inclusion	• Aged ≥ 18 years or Adolescents 12 – 18 years weighing > 40 kg • Lung involvement confirmed with chest imaging • Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization (may repeat test if > 4 days) • Willingness of study participant to accept randomization to any assigned treatment arm • Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study	Nausea Vomiting Elevated liver enzymes	PI: Onyema Ogbuagu Contact : Onyema.Ogbuagu@yale.edu Laurie.Andrews@yale.edu Contact (GH expanded access trial): Gavin.McLeod@greenwichhospital.org
		Key Exclusion	• Severe liver disease • SaO2/SPO2 ≤ 94% in room air condition, or the Pa02/Fi02 ratio < 300 mg Hg • Severe renal impairment or receiving renal replacement therapy • Pregnant or breastfeeding, or positive pregnancy test in a predose examination • Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation • Creatinine clearance < 50 mL/min		
	Severe Disease	Inclusion	• Aged ≥ 18 years or Adolescents 12 – 18 years weighing > 40 kg • Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization (may repeat test if > 4 days) • Peripheral capillary oxygen saturation (SpO2) ≤ 94% or requiring supplemental oxygen at screening		
		Key Exclusion	• Participation in any other clinical trial of an experimental treatment for COVID-19 • Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited < 24 hours prior to study drug dosing • Evidence of multiorgan failure • Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO • Requiring mechanical ventilation at screening • Severe liver disease • Creatinine clearance < 50 mL/min		

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 & on treatment dose heparin-based or fondaparinux anticoagulation • 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.