

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 4/3/20

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

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

A-Presence of:

Oxygen saturation $\leq 93\%$ on room air OR on chronic O₂ supplementation (if O₂>93% see box B)

YES

NO

START TREATMENT
(see treatment below)

SUPPORTIVE CARE &
EVERY 4 HOUR
OXYGEN MONITORING

Evaluate for Clinical Trials
(YNHH only)

NO

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*

YES

If Oxygen saturation $\leq 93\%$ on room air

TREATMENT

Start hydroxychloroquine x 5 days
Assess Clinical Trial Eligibility (YNHH only)

If ≥ 3 Liter O₂ requirement
OR ≥ 2 Liter O₂ requirement & hs-CRP >70
Consider **tocilizumab**

Consider **MICU evaluation** if > 4 Liter O₂ requirement or hemodynamic instability
(at YNHH see attached 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

***Immunosuppression** includes following: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone $\geq 20\text{mg}$ daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, and vasculitis.

COVID-SPECIFIC TESTS

- 1) Baseline & every 12 hours:** CRP, Troponin, D-dimer
- 2) Baseline & every 24 hours:** CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
- 3) Baseline & every 48 hours:** Cytokine panel, Angiotensin II level
- 4) Baseline EKG, and if not on telemetry, daily EKG.** (see appendix 1 for additional recommendations)
- 5) Repeat Chest X-Ray:** if clinical deterioration. (CXR **not** indicated for discharge or to document clinical improvement)

Cardiac: If significantly elevated troponin or EKG abnormalities and/or concern for CHF, consider TTE and cardiology input

Hematologic: All patients should receive prophylactic enoxaparin unless contraindicated (see appendix 3 for dosing recommendations)

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 4/3/20**

Respiratory failure, including **Mechanical ventilation and ECMO PLUS confirmed POSITIVE** SARS-CoV-2 by PCR

TREATMENT

Start Hydroxychloroquine x 5 days
Assess Clinical Trial Eligibility (YNHH only)



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



Consider **tocilizumab x 1 dose**
(in combination with hydroxychloroquine)



If progression in 48 hours despite tocilizumab
(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

Cardiac:

- Monitor electrolytes: **Replete Mg >2, K >4**
 - Baseline **EKG daily, monitor telemetry** closely for QTc Prolongation
 - 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
- (Appendix 1 for additional recommendations)

Hematologic:

- If **D-dimer < 10 mg/L:** All patients should receive **standard prophylactic enoxaparin** unless contraindicated*
 - If **D-dimer ≥10mg/L:** use **weight-based enoxaparin prophylaxis** 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 **confirmed VTE**, start therapeutic dose anticoagulation unless contraindicated*.
 - If signs of nasal or digital ischemia OR ferritin >100,000, consider Hematology consult at discretion of primary team
- (*see appendix 3 for dosing recommendations)

COVID-SPECIFIC TESTS

- 1) **Baseline & every 12 hours:** CRP, Troponin, D-dimer
- 2) **Baseline & every 24 hours:** CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
- 3) **Baseline & every 48 hours:** Cytokine panel, Angiotensin II level
- 4) **Baseline EKG**, and if not on telemetry, **daily EKG**. (see appendix 1 for additional recommendations)
- 5) **Repeat Chest X-Ray:** if clinical deterioration.

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	400mg PO q12h x 24h followed by 200mg q12h x 4 days for a 5 day total duration then re-assess	<ul style="list-style-type: none"> Prevents acidification of endosomes interrupting cellular functions and replication Prevents viral entry via ACE2 binding Reduction of viral infectivity Immunomodulator 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> QTc prolongation Rash Retinopathy is rare (Baseline eye exam is not required for use for COVID-19) 	<ul style="list-style-type: none"> 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 Therapy can be extended past 5 days based on patient's clinical response, but should not exceed 10 total days

IMMUNOMODULATING AGENTS

Tocilizumab¹⁰⁻¹³	8mg/kg IV x 1 dose (actual body weight); dose max 800 mg)	<ul style="list-style-type: none"> Monoclonal antibody to IL6 receptor 	<ul style="list-style-type: none"> IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease Retrospective data suggest possible benefit (clinical trials ongoing) 	<ul style="list-style-type: none"> Headache Elevated liver enzymes Infusion reactions (e.g. flushing, chills) 	<ul style="list-style-type: none"> The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time Additional doses not indicated at this time
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Medications which may be available through Clinical Trials

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

Remdesivir¹⁴⁻¹⁶	Clinical Trial dosing	<ul style="list-style-type: none"> Viral RNA dependent RNA polymerase inhibitor 	<ul style="list-style-type: none"> <i>In-vitro</i> data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit 	<ul style="list-style-type: none"> Nausea, vomiting, Elevated liver enzymes Rectal bleeding 	<ul style="list-style-type: none"> As of 3/22/20 remdesivir is available through clinical trials only and not through compassionate use except for pregnant patients and those < 18 years of age still have the option for compassionate use program Gilead is working on an expanded access program
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IMMUNOMODULATING AGENTS

Sarulimab ¹⁷⁻¹⁹	Clinical Trial dosing	<ul style="list-style-type: none"> • Monoclonal antibody to IL6 receptor 	<ul style="list-style-type: none"> • IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease 	<ul style="list-style-type: none"> • Elevated liver enzymes • Leukopenia • Infusion reactions (e.g. flushing, chills) 	<ul style="list-style-type: none"> • Available through clinical trial only at this time
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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 ^{8,20}	400mg/100 mg PO q24h x 5 days then reassess	<ul style="list-style-type: none"> • Viral protease inhibitor 	<ul style="list-style-type: none"> • In-vitro data reveals potent SARS-COV-2 inhibition 	<ul style="list-style-type: none"> • Limited availability, poor tolerability (such as GI side effects) and recent data demonstrated questionable clinical efficacy
Atazanavir²¹ NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir /ritonavir data¹⁹	400mg (2-200mg caps) PO q24h x 5 days then re-assess	<ul style="list-style-type: none"> • Viral protease inhibitor 	<ul style="list-style-type: none"> • More potent binding to the virus compared to other protease inhibitors <i>in vitro</i> (lower than lopinavir) • Drug more widely available than other PI's including lopinavir/ritonavir and better tolerated 	<ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ○ Atazanavir should be given 2 hours before or 1 hour after antacids ○ 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

<p>Azithromycin²²</p>	<p>500 mg x 1, followed by 250 mg q24h x 4 days</p>	<ul style="list-style-type: none"> • Not well defined; possible immunomodulator 	<ul style="list-style-type: none"> • In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load 	<ul style="list-style-type: none"> • Very limited data on use of azithromycin alone or in combination with other agents <ul style="list-style-type: none"> ○ 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
<p>Darunavir/Cobicistat²³</p>	<p>800 mg /150 mg PO q24h x 5 days</p>	<ul style="list-style-type: none"> • Viral protease inhibitor 	<ul style="list-style-type: none"> • In-vitro data shows SARS-COV-2 inhibition 	<ul style="list-style-type: none"> • Decreased binding to viral protease compared to atazanavir. No clinical data at this time
<p>Ribavirin²⁴⁻²⁶</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Viral RNA polymerase inhibitor and inhibition of elongation of RNA fragments 	<ul style="list-style-type: none"> • <i>In vitro</i> data for use in SARS-CoV and MERS-CoV indicates possible activity 	<ul style="list-style-type: none"> • 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
<p>Oseltamivir²⁷</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Inhibits influenza virus neuraminidase blocking viral release 	<ul style="list-style-type: none"> • Activity against influenza virus 	<ul style="list-style-type: none"> • 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
<p>Nitazoxanide²⁸</p>	<p>N/A</p>	<ul style="list-style-type: none"> • Augments host antiviral response 	<ul style="list-style-type: none"> • <i>In-vitro</i> data reveals SARS-COV-2 inhibition 	<ul style="list-style-type: none"> • No clinical data available

IMMUNOMODULATING AGENTS

<p>Interferon-beta²⁹⁻³¹</p>	<p>N/A</p>	<ul style="list-style-type: none"> Immunomodulator 	<ul style="list-style-type: none"> Possible activity against SARS-CoV and MERS-CoV Typically used in combination with ribavirin 	<ul style="list-style-type: none"> 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
<p>Corticosteroids³²⁻³⁶</p>	<p>If indicated per protocol: Methyl-prednisolone 40mg q8hr IV for three days, then re-assess</p>	<ul style="list-style-type: none"> Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression 	<ul style="list-style-type: none"> May be helpful in attenuating cytokine release in patients with severe disease 	<ul style="list-style-type: none"> Lack of effectiveness and potential harm shown in literature specifically inhibition of viral clearance in severe influenza and SARS³¹⁻³⁴, though possible benefit with critically ill COVID19 patients³⁵ May be considered for use by critical care team for salvage therapy <i>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</i>
<p>Intravenous immunoglobulin (IVIG)³⁷⁻³⁸</p>	<p>N/A</p>	<ul style="list-style-type: none"> Neutralizing antibodies against the virus 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Drug is on <i>critical national shortage</i> and has an unclear role as current preparations will not contain antibodies against SARS-CoV-2 at this time
<p>Baricitinib³⁹⁻⁴⁰</p>	<p>N/A</p>	<ul style="list-style-type: none"> Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase, may inhibit viral entry via endocytosis 	<ul style="list-style-type: none"> May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors 	<ul style="list-style-type: none"> Not available for off label use No clinical data available Risk of severe infections with use

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Appendix 1: Care Pathways for Mitigation of Drug-Induced Malignant Arrhythmias in COVID-19 Patients

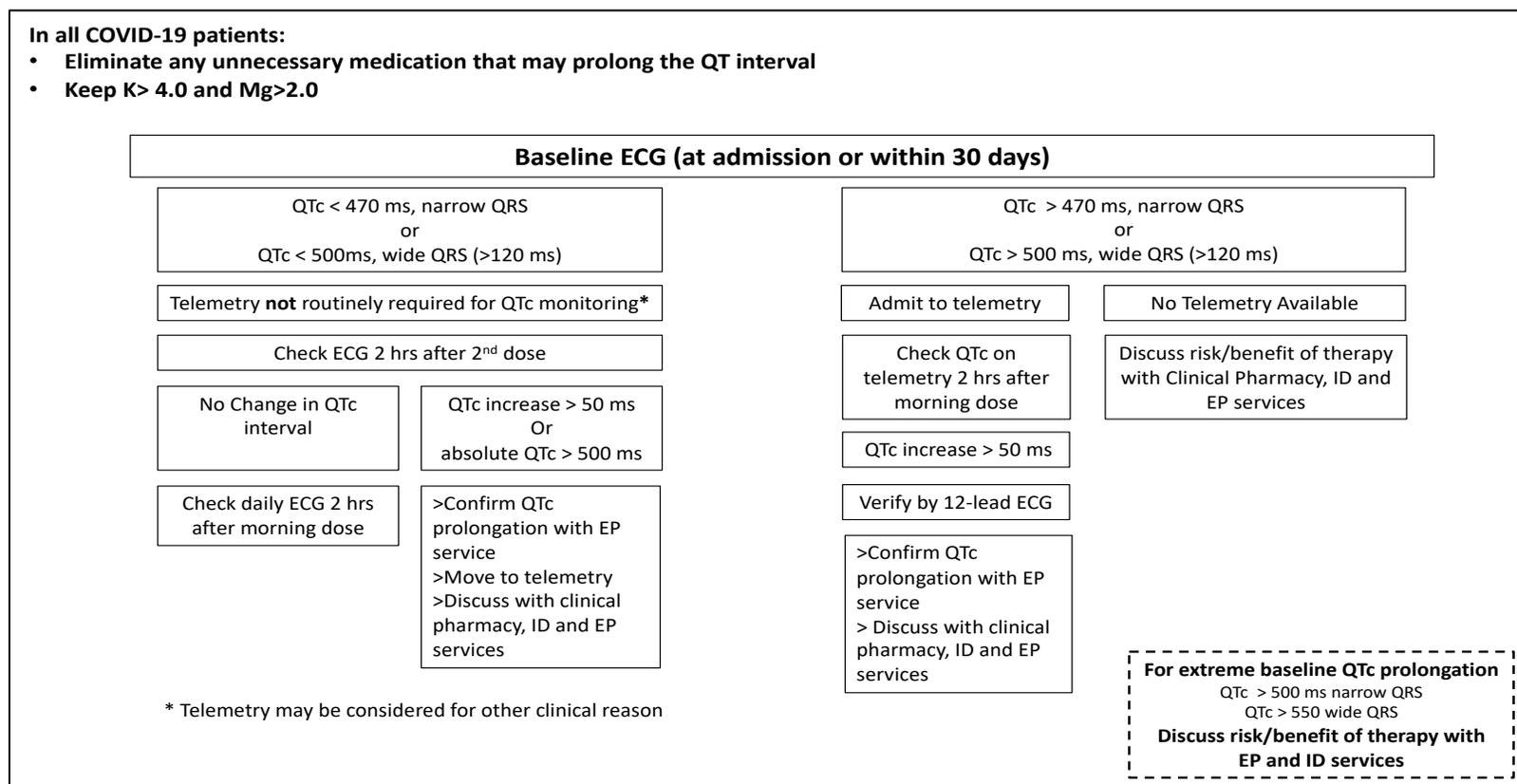
Recommendations:

All COVID-19 patients should have the following:

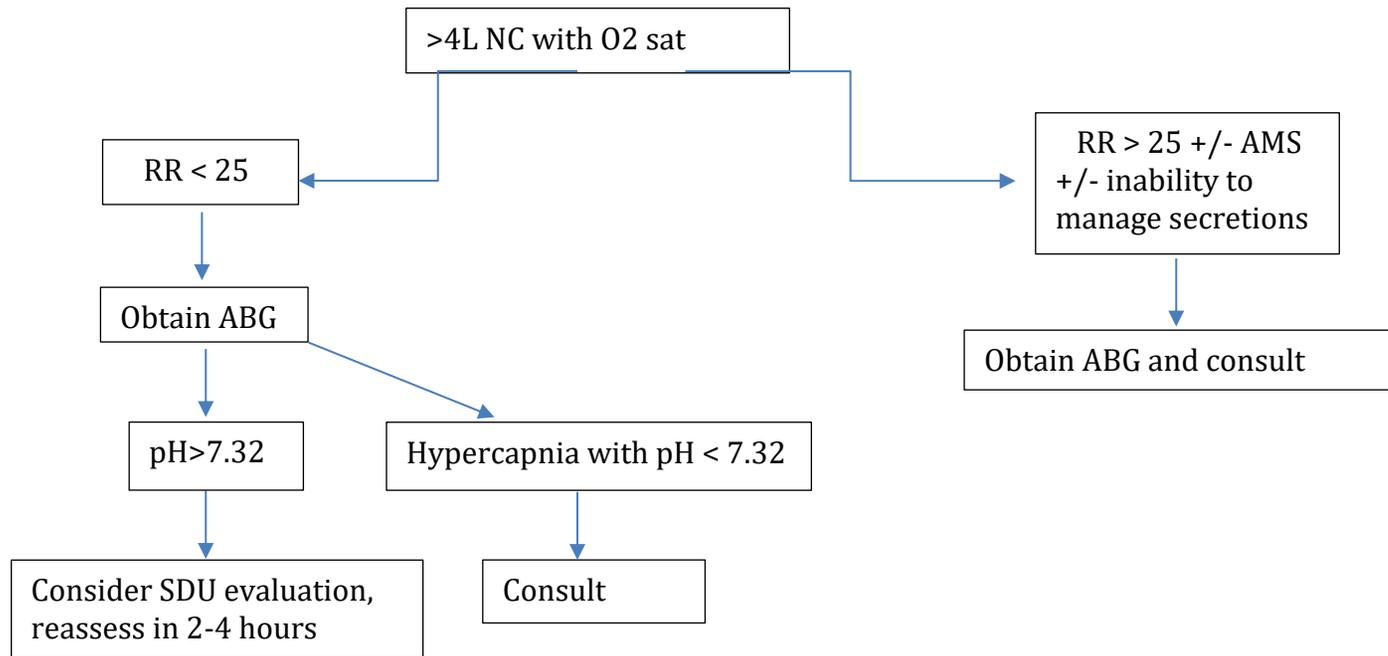
- When ordering an EKG for a COVID 19 patient to monitor their QTc, select the diagnosis “COVID 19” to alert cardiology to expedite the formal reading of the EKG.
- Daily monitoring of electrolytes; maintain K > 4 and Mg > 2
- All unnecessary QT prolonging drugs should be avoided or switched to alternatives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

Recommendations:

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



Appendix 2: YNHAcute Respiratory Failure with COVID- 19 MICU / SDU Triage Guidelines:



Appendix 3: Enoxaparin Dosing Guidelines:

All COVID-19 patients should receive VTE prophylaxis with enoxaparin unless contraindicated. If D-dimer > 10 mg/L and critically ill, increase to intermediate-dose weight-based VTE prophylaxis. If confirmed VTE, begin therapeutic enoxaparin unless contraindicated.

1) VTE prophylaxis in patients with D-dimer < 10 mg/L

- ❑ **CrCl ≥ 30 mL/min**
 - **BMI < 40 kg/m²**
 - Enoxaparin injection 40 mg sq daily
 - **BMI ≥ 40 kg/m²**
 - Enoxaparin injection 40 mg sq Q12H
- ❑ **CrCl < 30 mL/min:** Consult pharmacy and/or hematology for recommendations on enoxaparin dosing with anti-Xa level monitoring

2) If D-dimer ≥ 10 mg/L, increase to intermediate-dose weight-based VTE prophylaxis

- ❑ **Enoxaparin 0.5 mg/kg sq Q12H**
- ❑ **CrCl < 30 mL/min:** Consult pharmacy and/or hematology for enoxaparin with anti-Xa level monitoring

3) VTE Treatment- Confirmed VTE or high clinical suspicion for VTE

- ❑ **Enoxaparin 1 mg/kg sq Q12H**
- ❑ **CrCl < 30 mL/min:** Consult pharmacy and/or hematology for enoxaparin with anti-Xa level monitoring.