YNHHS Initial Treatment Algorithm for Hospitalized PATIENT 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 3/31/20

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

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

A-Presence of :
Oxygen saturation ≤ 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

Evaluate for Clinical Trials (YNHH only)

If **Oxygen saturation ≤ 93%** on room air → **START TREATMENT (see treatment below)**

B-Presence of:
1) Fever and/or **signs & symptoms of respiratory disease** (e.g. cough, dyspnea)
OR
2) Chest imaging showing pulmonary infiltrates

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
Assess Clinical Trial Eligibility (YNHH only)

If **≥ 3 Liter O2 requirement**
OR **any supplemental O2 requirement & hs-CRP >70**
Consider **tocilizumab**
Inform MICU and proceed to Severe algorithm

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

COVID-SPECIFIC TESTS
1) Draw at Baseline & every 12 hours:
CRP, CBC with differential, Ferritin, Procalcitonin, LDH, BNP, troponin, D-dimer, fibrinogen, PT/PTT
2) Draw at Baseline Only:
HIV-1/HIV-2 antibody/antigen.
3) Draw at baseline & every 48 hours:
Cytokine panel
4) Baseline EKG, and if not on telemetry**, daily EKG. (Appendix for addt'l recommendations)**
5) Repeat Chest X-Ray if clinical deterioration

***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, and vasculitis.

Cardiac: If troponin or BNP is abnormal, or new EKG changes, obtain TTE and consult cardiology

Hematologic: Give all patients weight-based prophylactic anticoagulation with enoxaparin unless contraindicated

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

YNHHS Initial Treatment Algorithm for Hospitalized PATIENTS 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 3/31/20

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

COVID-SPECIFIC TESTS
1) Draw at Baseline & every 12 hours:
CRP, CBC with differential, Procalcitonin, Ferritin, LDH, BNP troponin, D-dimer, fibrinogen, PT/PTT
2) Draw at Baseline Only:
HIV-1/HIV-2 antibody/antigen
3) Draw at baseline & every 48 hours:
Cytokine panel
4) Repeat CXR if clinical deterioration

Cardiac:
-Monitor electrolytes: **Replete Mg >2, K >4**
-Baseline **EKG daily, monitor telemetry** closely for QTc Prolongation
-Caution combining QTc prolonging medications
-If troponin or BNP are abnormal, or new EKG changes, obtain TTE and consult cardiology (Appendix for additional recommendations)

Hematologic:

-**All patients**: give prophylactic weight-based anticoagulation with enoxaparin unless contraindicated

- **If signs of nasal or digital ischemia OR ferritin >100,000** consider Hematology consult at discretion of primary team

-**If D-dimer >10mg/L** and **critically ill**, assess for presence of VTE and consider Hematology input. If confirmed VTE, begin therapeutic enoxaparin unless contraindicated.

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

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)[1-8]	400mg PO q12h x 24h followed by 200mg q12h x 4 days for a 5 day total duration then re-assess	• 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 • Therapy can be extended past 5 days based on patient's clinical response, but should not exceed 10 total days
IMMUNOMODULATING AGENTS					
Tocilizumab[9-12]	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)**					
Remdesevir[13-15]	***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 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

IMMUNOMODULATING AGENTS					
Sarulimab[16-18]	***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 <u>considered in certain cases</u> after discussion with Infectious Diseases and Pharmacy)

Drug	Dose	Mechanism	Rationale for possible efficacy	Rationale for NOT including as first line agent
Lopinavir/ Ritonavir[8,19]	400mg/100 mg PO q24h x 5 days then reassess	• 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[20]
 	
NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir /ritonavir data[18]
	400mg (2-200mg caps) PO q24h x 5 days then re-assess	• 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:
				  ○ 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

Azithromycin[21]	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[22]	800 mg /150 mg PO q24h x 5 days	• 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[23-25]	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[26]	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[27]	N/A	• Augments host antiviral response	• *In-vitro* data reveals SARS-COV-2 inhibition	• No clinical data available

IMMUNOMODULATING AGENTS				
Interferon-beta[28-30]	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 [31-35]	If indicated per algorithm: 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)[36-37]	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 [38-39]	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

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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.