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 4/13/20

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 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

Evaluate for Clinical Trials (YNHH only)

YES → **START TREATMENT**

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**
(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

***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

COVID-SPECIFIC TESTS

1) Baseline & every 12 hours: CRP, D-dimer, troponin (troponin x3 unless more testing is clinically indicated)

2) Baseline & every 24 hours: CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg

3) Baseline & ICU transfer: Cytokine panel

4) Baseline EKG, and if not on telemetry**, daily EKG x 3.** (see Appendix 3 for 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 4 for dosing recommendations)

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 4/13/20

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**
(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

COVID-SPECIFIC TESTS

1) Baseline & every 12 hours: CRP, D-dimer, troponin (troponin x3 unless more testing is clinically indicated)

2) Baseline & every 24 hours: CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg

3) Baseline & ICU admission: Cytokine panel

4) Baseline EKG, and if not on telemetry**, daily EKG x 3.** (see Appendix 3 for recommendations)

5) Repeat Chest X-Ray: if clinical deterioration. (CXR **not** indicated for discharge or to document clinical improvement)

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

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)

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, advanced liver cancer

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

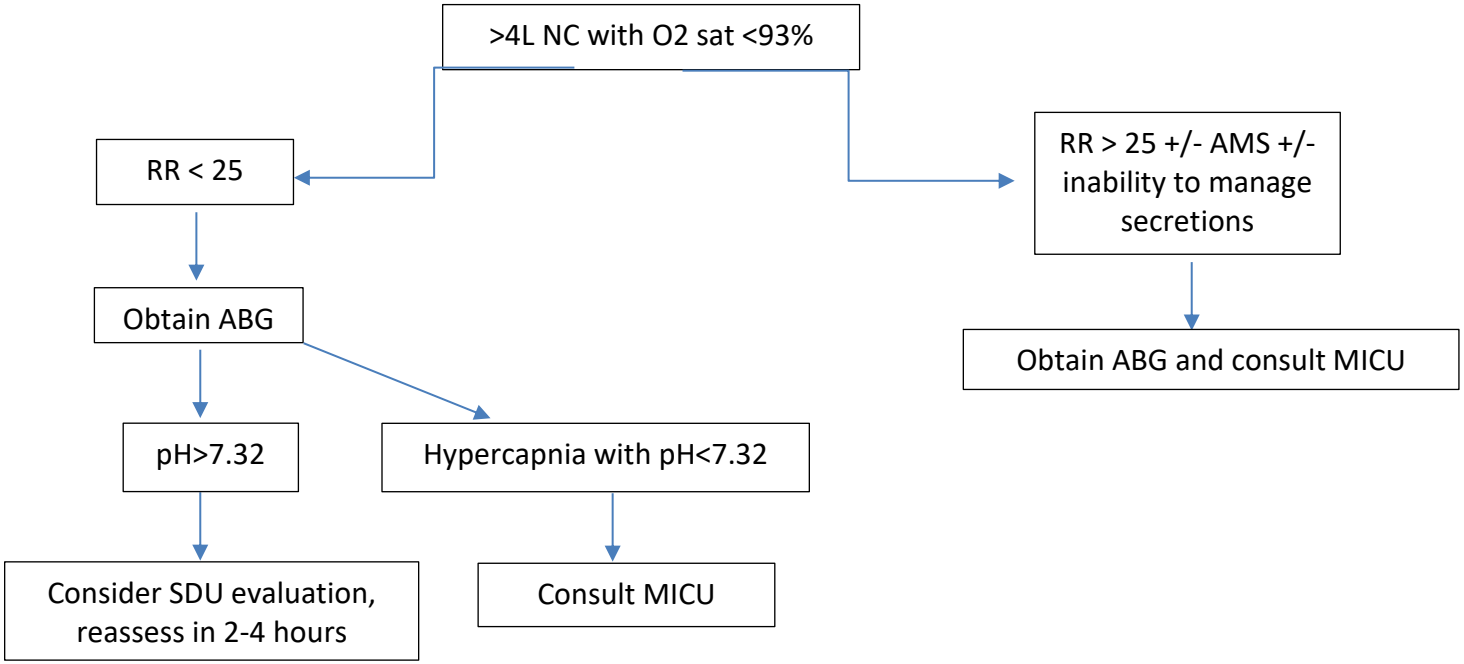
e. **Oncologic**: Advanced malignancy or high-grade primary brain tumors receiving only palliative treatment with estimated 3 or fewer month prognosis.

f. **Pulmonary**: Severe, chronic lung disease with baseline oxygen requirement of ≥ 60% FiO2; Primary pulmonary hypertension with NYHA Class III-IV heart failure (and patient refractory to/not a candidate for pulmonary vasodilators)

g. **Trauma**: Severe trauma; Severe burns: age >60 and 50% of total body surface area affected

h. **Functional Status**: Dependent in all ADLs due to a progressive chronic comorbid condition

Appendix 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

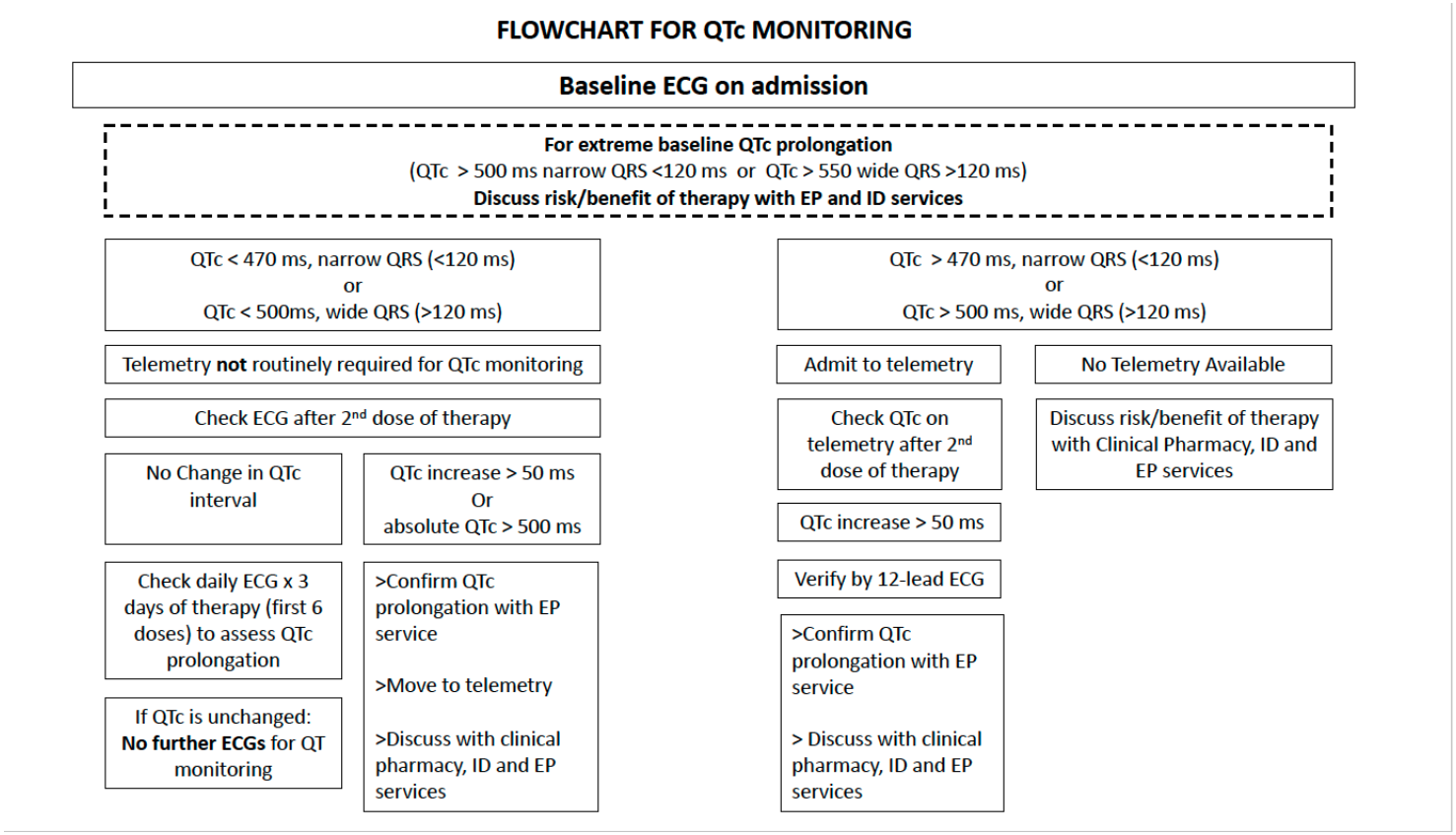
Recommendations:

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 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 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 Q12H	CrCl ≥ 30 mL/min • Enoxaparin 40mg sq Q12H CrCl < 30mL/min • Enoxaparin 40mg sq Q24H • Heparin 7500 units sq Q12H
≥ 5 mg/L **Intermediate Dose Prophylaxis**	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* • Apixaban CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H* • Apixaban • Heparin 7500 units sq Q12H	CrCl ≥ 30 mL/min • Enoxaparin 0.5mg/kg sq Q12H* • Apixaban CrCl < 30mL/min • Enoxaparin 0.5mg/kg sq Q12H* • Apixaban • Heparin 7500 units sq Q8H
Confirmed VTE or high clinical suspicion **TREATMENT**	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H • Apixaban CrCl < 30mL/min • Enoxaparin 1mg/kg sq Q24H • Apixaban • Therapeutic heparin	CrCl ≥ 30 mL/min • Enoxaparin 1mg/kg sq Q12H • Apixaban CrCl < 30mL/min • Enoxaparin 1mg/kg sq Q24H • Apixaban • Therapeutic heparin

Apixaban Dosing

DOAC	D-dimer ≥ 5 mg/L Intermediate Dose Prophylaxis	Confirmed VTE treatment or high clinical suspicion
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)

*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 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

*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]	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[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)**					
Remdesevir[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					
Sarulimab[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 <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[8,21]	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 RNA-dependent RNA polymerase.	• 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

		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).

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