**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

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**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)*

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**A-Presence of:**

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

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**START TREATMENT (see treatment below)**

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**B-Presence of:**

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

   OR

2) **Chest X-Ray** showing lung opacities

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**START TREATMENT**

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If **Oxygen saturation ≤ 93% on room air**

* For pregnant women, O₂ sat ≤ .95%

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**TREATMENT**

Start hydroxychloroquine x 5 days

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

  Consider tocilizumab
  (see Appendix 1 for exclusion criteria)

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

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**YNHH:** ID consult is not mandatory; consider ID input if immunosuppressed* or clinically decompensating

BH, GH, LMH, or WH: consult ID

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

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**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

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Report suspected adverse events related to therapeutics through RL solutions

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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

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

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

**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

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

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

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

Evaluation / Management of Secondary Causes of Respiratory Failure
- Vigorous pulmonary toillette
- Infection – blood and sputum cultures
- Pulmonary embolism
- Heart failure – limited TTE

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
- 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

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
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

Obtain ABG >4L NC with O2 sat <93%

RR < 25

Obtain ABG

pH>7.32

Hypercapnia with pH<7.32

Consult MICU

Consider SDU evaluation, reassess in 2-4 hours

RR > 25 +/- AMS +/- inability to manage secretions

Obtain ABG and consult MICU
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)

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 mg/L Prophylaxis</td>
<td>CrCl ≥ 30 mL/min &lt; 5 mg/L</td>
<td>CrCl ≥ 30 mL/min</td>
</tr>
<tr>
<td>Enoxaparin 40mg sq daily</td>
<td>Enoxaparin 40mg sq Q12H</td>
<td>Enoxaparin 40mg sq Q24H</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Enoxaparin 30mg sq daily</td>
<td>Enoxaparin 40mg sq Q24H</td>
<td>Enoxaparin 7500 units sq Q8-12H</td>
</tr>
<tr>
<td>Heparin 5000 units sq Q8-12H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 5 mg/L Intermediate Dose Prophylaxis</td>
<td>CrCl ≥ 30 mL/min</td>
<td>CrCl ≥ 30 mL/min</td>
</tr>
<tr>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
</tr>
<tr>
<td>DOAC</td>
<td>DOAC</td>
<td>DOAC</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>Enoxaparin 0.5mg/kg sq Q12H*</td>
</tr>
<tr>
<td>DOAC</td>
<td>DOAC</td>
<td>DOAC</td>
</tr>
<tr>
<td>Heparin 7500 units sq Q8-12H</td>
<td>Heparin 7500 units sq Q8H</td>
<td>Heparin 7500 units sq Q8H</td>
</tr>
</tbody>
</table>

**DOAC Dosing**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>D-dimer ≥ 5 mg/L Intermediate Dose Prophylaxis</th>
<th>Confirmed VTE treatment, high clinical suspicion or clotting of dialysis lines/tubing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>5mg PO Q12H regardless of renal function</td>
<td>10mg PO Q12H x 7 days followed by 5mg PO Q12H (limited data for 10mg in CrCl &lt; 25 or Cr &gt; 2.5)</td>
</tr>
<tr>
<td>Rivaroxaban (may favor in BMI ≥ 40kg/m2)</td>
<td>20mg Q24H Avoid use with CrCl &lt; 30 mL/min</td>
<td>15mg PO Q12H x 21 days followed by 20mg PO Q24H Avoid use with CrCl &lt; 30 mL/min</td>
</tr>
</tbody>
</table>

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

1Enoxaparin is the preferred form of anticoagulation

2Patients 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)

<table>
<thead>
<tr>
<th>D-dimer</th>
<th>BMI &lt; 40 kg/m²</th>
<th>BMI ≥ 40 kg/m²</th>
</tr>
</thead>
</table>
| < 3.5 mg/L  
Prophylaxis | CrCl ≥ 30 mL/min  
- Enoxaparin 40mg sq daily  
- 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
## Currently recommended medications for COVID-19
*(Subject to change as more data becomes available and based on medication availability)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Rationale for use</th>
<th>Notable Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
</table>
| Hydroxychloroquine (HCQ) | 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          | 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)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Trial dosing</th>
<th>Rationale for use</th>
<th>Notable Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
</table>
| Remdesivir | 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<sup>18-20</sup> | 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)*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Rationale for possible efficacy</th>
<th>Rationale for NOT including as first line agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ Ritonavir&lt;sup&gt;8,21&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Viral protease inhibitor</td>
<td>• In-vitro data reveals potent SARS-COV-2 inhibition</td>
<td>• Limited availability, poor tolerability (such as GI side effects) and recent data demonstrated questionable clinical efficacy</td>
</tr>
</tbody>
</table>

**Atzanavir<sup>22</sup>**

**NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir/ritonavir data<sup>19</sup>**

| 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 | • Atzanavir 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 Atzanavir should be given 2 hours before or 1 hour after antacids  
  o Atzanavir should be given at the same time as the H2 blocker or the atzanavir should be given 10 hours after or 2 hours before the H2 blocker | • For PPIs avoid concomitant use |
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Route</th>
<th>Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>500 mg x 1, followed by 250 mg q24h x 4 days</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Very limited data on use of azithromycin alone or in combination with other agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o Gautret, et al. study is limited by small sample size (only 6 patients received HCQ &amp; azithromycin combination) and those patients had lower viral loads than other included patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
</tr>
<tr>
<td>Darunavir/Cobicistat</td>
<td>N/A</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td>N/A</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Typically used with interferon</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Studied in patients with other coronaviruses with mixed results</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>N/A</td>
<td>• Inhibits influenza virus neuraminidase blocking viral release                      • Activity against influenza virus                                                           • No current data to support use of this drug.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Additionally, SARS-CoV-2 does not use neuraminidase in the replication cycle so mechanistically there would be no benefit</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>N/A</td>
<td>• Augments host antiviral response                                                  • In-vitro data reveals SARS-COV-2 inhibition                                              • No clinical data available</td>
<td></td>
</tr>
<tr>
<td><strong>IMMUNOMODULATING AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| Interferon-beta\(^{30-32}\) | N/A | • Immunomodulatory | • Limited data with SARS-CoV-2, toxicity risk outweighs benefit of use  
|  |  | • Possible activity against SARS-CoV and MERS-CoV |  
|  |  | • Typically used in combination with ribavirin | • Have been studied for patients with other coronaviruses with mixed results  
|  |  |  | • Not interferon-alpha or interferon-gamma  
| Corticosteroids\(^{33-37}\) |  | • Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression | • 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\(^{35}\).  
|  | If indicated per protocol: | • May be helpful in attenuating cytokine release in patients with severe disease | • May be considered for use by critical care team for salvage therapy  
|  | Methylprednisolone |  |  
|  | 40mg q8hr IV for three days, then re-assess |  |  
| Intravenous immunoglobulin (IVIG)\(^{38-39}\) | N/A | • Neutralizing antibodies against the virus | • 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  
|  |  | • 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 |  
| Baricitinib\(^{40-41}\) | N/A | • Janus Kinase (JAK) inhibitor binding cyclin G-associated kinase, may inhibit viral entry via endocytosis | • 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  
|  |  | • May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors |  
| Zinc\(^{42,43}\) | N/A | • Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as | • Not available for off label use  
|  |  | • Increasing intracellular zinc concentrations may inhibit RNA synthesis | • No clinical data available  
|  |  |  | • Risk of severe infections with use  
|  |  |  | • 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 | N/A | RNA-dependent RNA polymerase. Chloroquine has been demonstrated to be a zinc ionophore. All data is based on in vitro studies only. | • 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:

16. Clinical trials.gov (Identifier NCT04292899 and NCT04292730)
24. Clinicaltrials.gov (Identifier NCT04252274)
42. te Velthuis AJW, van den Worm, SHE, Sams AC, Baric RS, Snijder EJ, van Hemert MJ. Zn2+ 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.
## Appendix 6: Active Coronavirus (SARS-CoV)-2 infection Clinical Trials for Hospitalized Patients

<table>
<thead>
<tr>
<th>Drug, study description and rationale for use</th>
<th>Inclusion and Exclusion Criteria</th>
<th>Notable adverse effects</th>
<th>Primary Investigator(s)/Contact Information</th>
</tr>
</thead>
</table>
| **Drug: Remdesivir** | **Mild / Moderate Disease** | • 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 |
| **Viral RNA dependent RNA polymerase inhibitor** | **Inclusion** | • Severe liver disease  
• SaO2/SPO2 ≤ 94% in room air condition, or the PaO2/FiO2 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 | | |
| **Rationale:**  
In-vitro data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit | **Key Exclusion** | • 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 | | |
| **Description:**  
A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19 | **Severe Disease** | • 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 |

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<th>Inclusion</th>
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| • 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  
• Presence of neutropenia less than 2000/mm³  
• AST or ALT greater than 5 X ULN  
• Platelets < 50,000/mm³ |

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<th>Key Exclusion</th>
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| • Low likelihood of survival after 48 hours from screening  
• Presence of neutropenia less than 2000/mm³  
• AST or ALT greater than 5 X ULN  
• Platelets < 50,000/mm³ 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 |

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| • Aged ≥ 18 years  
• Confirmed positive SARS-CoV-2 infection by PCR  
• Severe or Life-threatening disease by the following definitions  
• Severe disease  
  • Requires 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 |

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<th>Relative Exclusion</th>
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| • ≥ 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 |

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**Contact:** Geoffrey.Chupp@yale.edu

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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.