**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 O2 supplementation (if O2>93% see box B)

**START TREATMENT** (see treatment below)

**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

**Does patient have:**
- Age ≥ 60
- BMI ≥ 30
- Diabetes (HgbA1c > 8.0)
- Chronic heart disease/HTN
- Chronic lung disease
- Immunosuppressed*

**START TREATMENT**

**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 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)*

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**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

---

**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

---

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

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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
**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

**Nephrology:**
- If acute kidney injury, check urinalysis and baseline urine protein/albumin.
- If ≥ 1 gram of protein, consider renal input

**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**

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**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 toilette
- 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 - 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 *

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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

- RR < 25
  - Obtain ABG
    - pH > 7.32
      - Consider SDU evaluation, reassess in 2-4 hours
    - Hypercapnia with pH < 7.32
      - Consult MICU
  - Hypercapnia with pH < 7.32

- >4L NC with O2 sat <93%
  - RR < 25
    - Obtain ABG
  - 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.

FLOWCHART FOR QTc MONITORING

Baseline ECG on admission

For extreme baseline QTc prolongation
(QTc > 500 ms narrow QRS <120 ms or QTc > 550 wide QRS >120 ms)
Discuss risk/benefit of therapy with EP and ID services

QTC < 470 ms, narrow QRS (<120 ms)
or
QTC < 500ms, wide QRS (>120 ms)
Telemetry not routinely required for QTc monitoring
Check ECG after 2nd dose of therapy
No Change in QTc interval
Check daily ECG x 3 days of therapy (first 6 doses) to assess QTc prolongation
If QTc is unchanged: No further ECGs for QT monitoring

QTC > 470 ms, narrow QRS (<120 ms)
or
QTC > 500 ms, wide QRS (>120 ms)
Admit to telemetry
Check QTc on telemetry after 2nd dose of therapy
QTc increase > 50 ms
Verify by 12-lead ECG
> Confirm QTc prolongation with EP service
> Move to telemetry
> Discuss with clinical pharmacy, ID and EP services

No Telemetry Available
Discuss risk/benefit of therapy with Clinical Pharmacy, ID and EP services

-
## 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><strong>&lt; 5 mg/L</strong></td>
<td><strong>Prophylaxis</strong></td>
<td><strong>Intermediate Dose Prophylaxis</strong></td>
</tr>
<tr>
<td>CrCl ≥ 30 mL/min</td>
<td>• Enoxaparin 40mg sq daily</td>
<td>• Enoxaparin 40mg sq Q12H</td>
</tr>
<tr>
<td>CrCl &lt; 30 mL/min</td>
<td>• Enoxaparin 30mg sq daily</td>
<td>• Enoxaparin 40mg sq Q24H</td>
</tr>
<tr>
<td>• Heparin 5000 units sq Q8-12H</td>
<td>• Heparin 7500 units sq Q8-12H</td>
<td></td>
</tr>
<tr>
<td><strong>≥ 5 mg/L</strong></td>
<td><strong>Intermediate Dose Prophylaxis</strong></td>
<td><strong>Confirmed VTE, high clinical suspicion, or clotting of dialysis lines/tubing</strong></td>
</tr>
<tr>
<td>CrCl ≥ 30 mL/min</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>• 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><strong>Apixaban</strong></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><strong>Rivaroxaban</strong></td>
<td>20mg Q24H</td>
<td>15mg PO Q12H x 21 days followed by 20mg PO Q24H</td>
</tr>
<tr>
<td>(may favor in BMI ≥ 40 kg/m²)</td>
<td>Avoid use with CrCl &lt; 30 mL/min</td>
<td>Avoid use with CrCl &lt; 30 mL/min</td>
</tr>
</tbody>
</table>

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

1. Enoxaparin is the preferred form of anticoagulation
2. Patients receiving treatment should continue full dose anticoagulation for 3 months
3. 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>
<tbody>
<tr>
<td>&lt; 3.5 mg/L</td>
<td>CrCl ≥ 30 mL/min</td>
<td>CrCl ≥ 30 mL/min</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>• Enoxaparin 40mg sq daily</td>
<td>• Enoxaparin 40mg sq Q12H</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 mL/min</td>
<td>CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>• Enoxaparin 30mg sq daily</td>
<td>• Enoxaparin 40mg sq Q24H</td>
</tr>
</tbody>
</table>

| ≥ 3.5 mg/L  | CrCl ≥ 30 mL/min  | CrCl ≥ 30 mL/min  |
| Intermediate Dose Prophylaxis | • Enoxaparin 0.5mg/kg sq Q12H* | • Enoxaparin 0.5mg/kg sq Q12H* |
|           | CrCl < 30 mL/min | CrCl < 30 mL/min |
|           | • Enoxaparin 0.5mg/kg sq Q12H* | • Enoxaparin 0.5mg/kg sq Q12H* |

| ≥ 7 mg/L  | CrCl ≥ 30 mL/min  | CrCl ≥ 30 mL/min  |
| Confirmed VTE or high clinical suspicion | • Enoxaparin 1mg/kg sq Q12H | • Enoxaparin 1mg/kg sq Q12H |
| Treatment | CrCl < 30 mL/min | CrCl < 30 mL/min |
|           | • Enoxaparin 1mg/kg sq Q24H | • 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 |
| **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**

<table>
<thead>
<tr>
<th>Sarilumab&lt;sup&gt;18-20&lt;/sup&gt;</th>
<th>Clinical Trial dosing</th>
<th>Monoclonal antibody to IL6 receptor</th>
<th>IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease</th>
<th>Elevated liver enzymes</th>
<th>Leukopenia</th>
<th>Infusion reactions (e.g. flushing, chills)</th>
<th>Available through clinical trial only at this time</th>
</tr>
</thead>
</table>

**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><strong>Lopinavir/Ritonavir</strong>&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>
<tr>
<td><strong>Atazanavir</strong>&lt;sup&gt;22&lt;/sup&gt; NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir/ritonavir data&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N/A</td>
<td>Viral protease inhibitor</td>
<td>More potent binding to the virus compared to other protease inhibitors <em>in vitro</em> (lower than lopinavir)</td>
<td>Mild indirect hyperbilirubinemia is common and not indicative of hepatic dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug more widely available than other PI’s including lopinavir/ritonavir and better tolerated</td>
<td>CYP enzyme inhibitor (3A4, 2C8) monitor/discuss with pharmacy potential for drug-drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For patients with NG/OG/NJ open capsules for enteral administration</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Atazanavir needs an acidic environment for absorption and therefore <em>antacids, H2 blockers, proton pump inhibitors (PPIs) should be avoided.</em> If these agents must be given the administration should be separated as below:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>o Atazanavir should be given 2 hours before or 1 hour after antacids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For PPIs avoid concomitant use</td>
</tr>
</tbody>
</table>

*PPIs: Proton pump inhibitors*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Indications</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</td>
<td>• In a small study, combination of HCQ and azithromycin was associated with significant reduction in SARS-CoV-2 viral load</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/</td>
<td>N/A</td>
<td>• Viral protease inhibitor</td>
<td>• In-vitro data shows SARS-COV-2 inhibition</td>
</tr>
<tr>
<td>Cobicistat</td>
<td></td>
<td></td>
<td>• Decreased binding to viral protease compared to atazanavir. No clinical data at this time</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>N/A</td>
<td>• Viral RNA polymerase inhibitor and inhibition of elongation of RNA fragments</td>
<td>• In vitro data for use in SARS-CoV and MERS-CoV indicates possible activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use</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>Oseltimivir</td>
<td>N/A</td>
<td>• Inhibits influenza virus neuraminidase blocking viral release</td>
<td>• Activity against influenza virus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No current data to support use of this drug.</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</td>
<td>• No clinical data available</td>
</tr>
<tr>
<td>IMMUNOMODULATING AGENTS</td>
<td>Interferon-beta</td>
<td>N/A</td>
<td>• Immunomodulator</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------</td>
<td>-----</td>
<td>---------------------</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>If indicated per protocol: Methylprednisolone 40mg q8hr IV for three days, then re-assess</td>
<td>• Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression</td>
<td>• May be helpful in attenuating cytokine release in patients with severe disease</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG) 38-39</td>
<td>N/A</td>
<td>• Neutralizing antibodies against the virus</td>
<td>• May have both antiviral and immunomodulatory effects</td>
</tr>
<tr>
<td>Baricitinib 40-41</td>
<td>N/A</td>
<td>• Janus Kinase (JAK) inhibitor binding cyclin G - associated kinase, may inhibit viral entry via endocytosis</td>
<td>• May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors</td>
</tr>
<tr>
<td>Zinc 42,43</td>
<td>N/A</td>
<td>• Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as</td>
<td>• Increasing intracellular zinc concentrations may inhibit RNA synthesis</td>
</tr>
<tr>
<td>Ascorbic acid &amp; Thiamine</td>
<td>RNA-dependent RNA polymerase. Chloroquine has been demonstrated to be a zinc ionophore. All data is based on in vitro studies only.</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

| References: |

16. Clinical trials.gov (Identifier NCT04292899 and NCT04292730)
24. Clinicaltrials.gov (Identifier NCT04252274)
42. te Velthuis AJW, van den Worm, SHE, Sims 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** | • 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  
• 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 | Nausea  
Vomiting  
Elevated liver enzymes | **PI:** Onyema Ogbuagu  
**Contact:**  
[Onyema.Ogbuagu@yale.edu](mailto:Onyema.Ogbuagu@yale.edu)  
[Laurie.Andrews@yale.edu](mailto:Laurie.Andrews@yale.edu)  
**Contact (GH expanded access trial):**  
[Gavin.McLeod@greenwichhospital.org](mailto:Gavin.McLeod@greenwichhospital.org) |
<p>| <strong>Mild / Moderate Disease</strong> | <strong>Inclusion</strong> |  |  |
| <strong>Key Exclusion</strong> |  |  |  |
| <strong>Severe Disease</strong> | <strong>Inclusion</strong> |  |  |
| <strong>Key Exclusion</strong> |  |  |  |</p>
<table>
<thead>
<tr>
<th>Drug: Sarilumab</th>
<th>Inclusion</th>
<th>Key Exclusion</th>
</tr>
</thead>
</table>
| Monoclonal antibody to IL-6 receptor | • 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 | Elevates liver enzymes  
Leukopenia  
Infusion reactions (e.g. flushing, chills) |
| **Rationale:**  
IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease | • 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 | |
| **Description:**  
Phase 2/3, Randomized, Double-Blind, Placebo Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19 | |

<table>
<thead>
<tr>
<th>Expanded access program for use of convalescent plasma in COVID-19 patients</th>
<th>Inclusion</th>
<th>Relative Exclusion</th>
</tr>
</thead>
</table>
| • Aged ≥ 18 years  
• Confirmed positive SARS-CoV-2 infection by PCR  
• Severe or Life-threatening disease by the following definitions  
• Severe disease  
  o 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  
  o Refractory respiratory failure, or  
  o Septic shock, or  
  o Multi-organ dysfunction | • ≥ 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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LMH/WH: Christopher.Song@lmhosp.org  

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