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 5/8/20

Patient with confirmed POSITIVE SARS-CoV-2 by PCR
Assess all patients routinely for clinical trial eligibility (see Appendix 1)
*(If mechanically ventilated or on ECMO, proceed to Severe algorithm)

- Oxygen saturation ≤ 94% on room air (≤ 95% if pregnant)

**YES**
Continue supportive care
Consider adjunctive treatment

**NO**
SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING

### ADJUNCTIVE TREATMENT CONSIDERATIONS

- Consider hydroxychloroquine x 5 days with close cardiac monitoring (see Appendix 2)

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

Tocilizumab x 1 dose
(see Appendix 3 for exclusion criteria)

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

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

- Report suspected adverse events related to therapeutics through RL solutions

### 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 2 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 5/8/20

Patient with **confirmed POSITIVE** SARS-CoV-2 by PCR
Assess all patients routinely for clinical trial eligibility (see Appendix 1)

---

**Continue supportive care**
**Consider adjunctive treatment**

**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 2 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 ≥ 3 Liter O2 requirement**
**OR ≥ 2 Liter O2 requirement & hs-CRP >70**
**Tocilizumab** x 1 dose
(see Appendix 3 for exclusion criteria)

---

If **worsening ARDS** after 48 hours:

**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

---

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

---

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

Report suspected adverse events related to therapeutics through **RL solutions**

---

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
**YNHHS Initial Treatment Algorithm for** [Hospitalized ADULTS with 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 5/8/20**

### Hematologic:
- If D-dimer < 5 mg/L: All patients should receive standard prophylactic anticoagulation and aspirin 81mg daily unless contraindicated★
- If D-dimer ≥ 5mg/L or receiving convalescent plasma: use weight-based intermediate prophylactic anticoagulation and aspirin 81mg daily unless contraindicated★
- If confirmed VTE or high clinical suspicion, start therapeutic dose anticoagulation and aspirin 81mg daily 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 5 for anticoagulation dosing recommendations)

Aspirin 81mg PO daily
- Relative contraindications: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder
- Discontinue at discharge

### Cardiac:
- Monitor electrolytes: **Replete Mg >2, K >4**
- Baseline EKG and monitor telemetry closely for QTc Prolongation (Appendix 2 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 5b)

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

### Immunosuppressed hosts include:
- 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 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 5/8/20

Guidance for Patients with Confirmed COVID-19 and Refractory Respiratory Failure Requiring ECMO

Prior to cannulation
- Goals of care discussion
- Follow YNHHS COVID-19 Severe Algorithm for treatment and testing
- Evaluate for secondary causes of respiratory failure
- Order pre-ECMO cytokine panel

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

ECMO (24-48 hours)
- Order post-ECMO cytokine panel (after ~48 hours)
- Assess eligibility for clinical trials / expanded access protocols

Potential Adjunctive Therapeutic Resources
- Convalescent plasma administration if eligible
- Consult Allergy / Immunology to help target immune dysregulation
  - Sarilumab trial if eligible (current trial excludes patients who received an IL-6 antagonist in the prior 30 days)
  - Possible repeat tocilizumab dosing
- Cytokine adsorption via ECMO circuit

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

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
## Appendix 1: 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>
<tbody>
<tr>
<td><strong>Drug: Remdesivir</strong></td>
<td></td>
<td></td>
<td>Pl: Onyema Ogbuagu</td>
</tr>
<tr>
<td>Viral RNA dependent RNA polymerase inhibitor</td>
<td></td>
<td></td>
<td>Contact: <a href="mailto:Onyema.Ogbuagu@yale.edu">Onyema.Ogbuagu@yale.edu</a></td>
</tr>
<tr>
<td><strong>Rationale:</strong></td>
<td></td>
<td></td>
<td><a href="mailto:Laurie.Andrews@yale.edu">Laurie.Andrews@yale.edu</a></td>
</tr>
<tr>
<td>In-vitro data reveals potent SARS-CoV-2 inhibition and early clinical data shows possible benefit</td>
<td></td>
<td></td>
<td>Contact (GH expanded access trial): <a href="mailto:Gavin.McLeod@greenwichtospital.org">Gavin.McLeod@greenwichtospital.org</a></td>
</tr>
<tr>
<td><strong>Description:</strong> A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Mild / Moderate Disease</strong></td>
<td>• Aged ≥ 18 years or Adolescents 12 – 18 years weighing &gt; 40 kg</td>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lung involvement confirmed with chest imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization (may repeat test if &gt; 4 days)</td>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Willingness of study participant to accept randomization to any assigned treatment arm</td>
<td>Elevated liver enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Must agree not to enroll in another study of an investigational agent prior to completion of Day 28 of study</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Exclusion</strong></td>
<td>• Severe liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• SaO2/SPO2 ≤ 94% in room air condition, or the PaO2/FiO2 ratio &lt; 300 mg Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe renal impairment or receiving renal replacement therapy</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Pregnant or breastfeeding, or positive pregnancy test in a predose examination</td>
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<tr>
<td></td>
<td>• Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Creatinine clearance &lt; 50 mL/min</td>
<td></td>
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</tr>
<tr>
<td><strong>Severe Disease</strong></td>
<td>• Aged ≥ 18 years or Adolescents 12 – 18 years weighing &gt; 40 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test ≤ 4 days before randomization (may repeat test if &gt; 4 days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Peripheral capillary oxygen saturation (SpO2) ≤ 94% or requiring supplemental oxygen at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Key Exclusion</strong></td>
<td>• Participation in any other clinical trial of an experimental treatment for COVID-19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 is prohibited &lt; 24 hours prior to study drug dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Evidence of multiorgan failure</td>
<td></td>
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<tr>
<td></td>
<td>• Mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Requiring mechanical ventilation at screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Creatinine clearance &lt; 50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug</strong>: Sarilumab</td>
<td><strong>Inclusion</strong></td>
<td><strong>Contact</strong>: Geoffrey Chupp Contact: <a href="mailto:Geoffrey.Chupp@yale.edu">Geoffrey.Chupp@yale.edu</a></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------</td>
<td></td>
</tr>
</tbody>
</table>
| Monoclonal antibody to IL6 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* | Elevated 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 | **Key Exclusion** | |
| **Inclusion** | *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* | **Expanded access program for use of convalescent plasma in COVID-19 patients** |
| **Relative Exclusion** | * ≥ 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*  
*Known severe IgA deficiency* | *Contacts*:  
YNHH: Mahalia.desruisseaux@yale.edu  
BH: Tina.McCurry@bpthosp.org  
GH: James.Sabetta@greenwichhospital.org  
LMH/WH: Christopher.Song@lmhosp.org |
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.
Appendix 2: 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 3: 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 4: 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
  - >4L NC with O2 sat < 93%

- RR > 25 +/- AMS +/- inability to manage secretions
  - Obtain ABG and consult MICU
Appendix 5a: Anticoagulation Dosing Guidelines (Non-Pregnant Patients)*

Administer aspirin 81mg PO daily to all patients unless contraindicated. Discontinue aspirin at discharge.

<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></td>
<td></td>
</tr>
<tr>
<td><strong>CrCl ≥ 30 mL/min</strong></td>
<td>- Enoxaparin 40mg sq daily</td>
<td></td>
</tr>
<tr>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td>- Enoxaparin 30mg sq daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Heparin 5000 units sq Q8-12H</td>
<td></td>
</tr>
<tr>
<td>≥ 5 mg/L or receiving convalescent plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate Dose Prophylaxis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CrCl ≥ 30 mL/min</strong></td>
<td>- Enoxaparin 0.5mg/kg sq Q12H*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- DOAC</td>
<td></td>
</tr>
<tr>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td>- Enoxaparin 0.5mg/kg sq Q12H*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- DOAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Heparin 5000 units sq Q8-12H</td>
<td></td>
</tr>
<tr>
<td>Confirmed VTE, high clinical suspicion, or clotting of dialysis lines/tubing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TREATMENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CrCl ≥ 30 mL/min</strong></td>
<td>- Enoxaparin 1mg/kg sq Q12H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- DOAC</td>
<td></td>
</tr>
<tr>
<td><strong>CrCl &lt; 30 mL/min</strong></td>
<td>- Enoxaparin 1mg/kg sq Q24H</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- DOAC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Therapeutic heparin</td>
<td></td>
</tr>
</tbody>
</table>

**DOAC Dosing**

<table>
<thead>
<tr>
<th>DOAC</th>
<th>D-dimer ≥ 5 mg/L</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>Intermediate Dose Prophylaxis</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></td>
<td>5mg PO Q12H regardless of renal function</td>
<td></td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>(may favor in BMI ≥ 40 kg/m2)</td>
<td>15mg PO Q12H x 21 days followed by 20mg PO Q24H Avoid use with CrCl &lt; 30 mL/min</td>
</tr>
<tr>
<td></td>
<td>20mg Q24H Avoid use with CrCl &lt; 30 mL/min</td>
<td></td>
</tr>
</tbody>
</table>

*Enoxaparin is the preferred form of anticoagulation

þRelative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

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

†Patients 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 5b: Anticoagulation Dosing Guidelines (Pregnant Patients)

Administer aspirin 81mg PO daily to all patients unless contraindicated. Discontinue aspirin at discharge.

<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 Prophylaxis</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 40mg sq daily&lt;br&gt;CrCl &lt; 30mL/min&lt;br&gt;– Enoxaparin 30mg sq daily</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 40mg sq Q12H&lt;br&gt;CrCl &lt; 30mL/min&lt;br&gt;– Enoxaparin 40mg sq Q24H</td>
</tr>
<tr>
<td>≥ 3.5 mg/L or receiving convalescent plasma Intermediate Dose Prophylaxis</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 0.5mg/kg sq Q12H&lt;br&gt;CrCl &lt; 30mL/min&lt;br&gt;– Enoxaparin 0.5mg/kg sq Q12H*</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 0.5mg/kg sq Q12H*</td>
</tr>
<tr>
<td>≥ 7 mg/L Confirmed VTE or high clinical suspicion TREATMENT</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 1mg/kg sq Q12H&lt;br&gt;CrCl &lt; 30mL/min&lt;br&gt;– Enoxaparin 1mg/kg sq Q24H</td>
<td>CrCl ≥ 30 mL/min&lt;br&gt;– Enoxaparin 1mg/kg sq Q12H&lt;br&gt;CrCl &lt; 30mL/min&lt;br&gt;– Enoxaparin 1mg/kg sq Q24H</td>
</tr>
</tbody>
</table>

Dosing weight for PREGNANT patients should be actual body weight and POST-PARTUM dosing should be PRE-PREGNANCY weight

*Relative contraindications for aspirin: recent or risk for CNS bleed, use of other anti-platelet therapy, severe thrombocytopenia, allergy, or history of bleeding disorder

*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 6

## Possible 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) | • Administration of HCQ should be considered on an individual patient basis by the primary inpatient provider.  
• Monitor for QTc prolongation. See Appendix 2 above.  
• For patients with NG/OG/NT hydroxychloroquine can be crushed for enteral administration |
| Tocilizumab               | 8mg/kg IV x 1 dose (actual body weight; dose max 800mg)            | • 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 |

### IMMUNOMODULATING AGENTS

| Remdesivir               | 200mg IV once followed by 100mg IV daily for 5 or 10 days          | • 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 | • Remdesivir was authorized (not approved) by the FDA through an Emergency Use Authorization (EUA) dated 5/1/2020 but is not yet available to the YNHHS  
• Remdesivir remains available through clinical trials |
| Convalescent Plasma      | One ABO compatible unit                                            | • Individual (not pooled) plasma from a recovered COVID19 patient                                                                         | • Transfer of potentially neutralizing antibodies which could diminish viral pathogenesis | • Transfusion reactions  
• Potential to increase hypercoagulability | • Available through expanded access, not a trial  
• Each unit may contain variable titers of anti-SARS-CoV-2 antibodies with differing avidity  
• Cannot be used in patients with IgA deficiency due to risk of anaphylaxis  
• Use with intermediate dosing anticoagulation (see Appendix 5 above) |
**IMMUNOMODULATING AGENTS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Clinical Trial dosing</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>Sarilumab</td>
<td></td>
<td>Clinical Trial dosing</td>
<td>• Monoclonal antibody to IL6 receptor</td>
<td>IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease</td>
<td>• Elevated liver enzymes</td>
</tr>
</tbody>
</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>Lopinavir/</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>Ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(32-35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</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>(36)</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 <strong>antacids, H2 blockers, proton pump inhibitors (PPIs) should be avoided.</strong> 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>

*For PPIs avoid concomitant use*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/Route</th>
<th>Mechanism of Action</th>
<th>Clinical Data</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>• Very limited data on use of azithromycin alone or in combination with other agents</td>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td></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        • In vitro data for use in SARS-CoV and MERS-CoV indicates possible activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Typically used with interferon</td>
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<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</td>
<td></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                                                  • In-vitro data reveals SARS-COV-2 inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No clinical data available</td>
</tr>
</tbody>
</table>

*HCQ* = Hydroxychloroquine, *SARS-CoV-2* = Severe Acute Respiratory Syndrome Coronavirus 2, *MERS-CoV* = Middle East Respiratory Syndrome Coronavirus
<table>
<thead>
<tr>
<th>IMMUNOMODULATING AGENTS</th>
</tr>
</thead>
</table>
| **Interferon-beta**  
(33-35, 43) | 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**  
(44-48) | If indicated per protocol: Methylprednisolone  
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)**  
(49, 50) | 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**  
(51, 52) | 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**  
(53, 54) | 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 |
<table>
<thead>
<tr>
<th>Ascorbic acid &amp; Thiamine (55-58)</th>
<th>N/A</th>
<th>• Unclear; ?role in septic shock/ARDS</th>
<th>• ? benefit in septic shock/ARDS</th>
</tr>
</thead>
</table>

References:

20. Sciences G. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19). NCT042928992020.
21. Sciences G. Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Moderate Coronavirus Disease (COVID-19) Compared to Standard of Care Treatment. NCT042927302020.