YNHHS Initial Treatment Algorithm for Hospitalized ADULTS with Non-Severe* COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted – Algorithm last updated 4/13/20

Patient with confirmed POSITIVE SARS-CoV-2 by PCR *(If mechanically ventilated or on ECMO, proceed to Severe algorithm)

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

B-Presence of:
1) Fever and/or signs & symptoms of respiratory disease (e.g. cough, dyspnea) OR
2) Chest X-Ray showing lung opacities

START TREATMENT (see treatment below)

SUPPORTIVE CARE & EVERY 4 HOUR OXYGEN MONITORING
Evaluate for Clinical Trials (YNHH only)

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

If Oxygen saturation ≤ 93% on room air

TREATMENT
Start hydroxychloroquine x 5 days
Assess Clinical Trial Eligibility (YNHH only)

If ≥ 3 Liter O₂ requirement
OR ≥ 2 Liter O₂ requirement & hs-CRP >70
Consider tocilizumab
(see Appendix 1 for exclusion criteria)

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

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

*Immunosuppression includes following: Cancer treatment within 1 year, the use of immunosuppressive drugs (biologics, chronic prednisone ≥20mg daily), solid organ transplant, bone marrow transplantation, HIV/AIDS (regardless of CD4 count), leukemia, lymphoma, SLE, vasculitis, and pregnancy

COVID-SPECIFIC TESTS
1) Baseline & every 12 hours: CRP, D-dimer, troponin (troponin x3 unless more testing is clinically indicated)
2) Baseline & every 24 hours: CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
3) Baseline & ICU transfer: Cytokine panel
4) Baseline EKG, and if not on telemetry, daily EKG x 3. (see Appendix 3 for recommendations)
5) Repeat Chest X-Ray: if clinical deterioration. (CXR not indicated for discharge or to document clinical improvement)

Cardiac: If significantly elevated troponin or EKG abnormalities and/or concern for CHF, consider TTE and cardiology input

Hematologic: All patients should receive prophylactic enoxaparin unless contraindicated (see Appendix 4 for dosing recommendations)

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
YNHHS Initial Treatment Algorithm for Hospitalized ADULTS with Severe COVID-19

Disclaimer: There are no FDA-approved treatments for COVID-19, supportive care is standard of care. Limited treatment data are available & clinical judgment is warranted - Algorithm last updated 4/13/20

Respiratory failure, including Mechanical ventilation and ECMO PLUS confirmed POSITIVE SARS-CoV-2 by PCR

**TREATMENT**

Start Hydroxychloroquine x 5 days
Assess Clinical Trial Eligibility (YNHH only)

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

**Cardiac:**
- Monitor electrolytes: Replete Mg >2, K >4
- Baseline EKG and monitor telemetry closely for QTc Prolongation (Appendix 3 for recommendations)
- Caution combining QTc prolonging medications
- If significantly elevated troponin or EKG abnormalities and/or hemodynamic instability, consider POCUS for LV function assessment and cardiology consult

**Hematologic:**
- If D-dimer <5 mg/L: All patients should receive **standard prophylactic anticoagulation** unless contraindicated*
- If D-dimer ≥5mg/L: use weight-based **intermediate prophylactic anticoagulation** unless contraindicated*
- If confirmed VTE or high clinical suspicion, start **therapeutic dose anticoagulation** unless contraindicated*
- If sudden and unexplained change in O2 or new asymmetrical upper or lower extremity edema, consider venous U/S of affected extremity
- If ferritin >100,000 or D-dimer >10mg/L, consider Hematology consult at discretion of primary team
  (*see Appendix 4 for dosing recommendations)

**COVID-SPECIFIC TESTS**

1) Baseline & every 12 hours: CRP, D-dimer, troponin (troponin x3 unless more testing is clinically indicated)
2) Baseline & every 24 hours: CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
3) Baseline & ICU admission: Cytokine panel
4) Baseline EKG, and if not on telemetry, daily EKG x 3. (see Appendix 3 for recommendations)
5) Repeat Chest X-Ray: if clinical deterioration. (CXR not indicated for discharge or to document clinical improvement)

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
  - Hypercapnia with pH < 7.32
    - Consider SDU evaluation, reassess in 2-4 hours
    - Consult MICU

- >4L NC with O2 sat < 93%
- Consult MICU

- 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
# 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>
</table>
| < 5 mg/L Prophylaxis | CrCl ≥ 30 mL/min  
  • Enoxaparin 40mg sq daily  
  • Enoxaparin 30mg sq daily  
  • Heparin 5000 units sq Q12H | CrCl ≥ 30 mL/min  
  • Enoxaparin 40mg sq Q12H  
  • Enoxaparin 40mg sq Q24H  
  • Heparin 7500 units sq Q12H |
| ≥ 5 mg/L Intermediate Dose Prophylaxis | CrCl ≥ 30 mL/min  
  • Enoxaparin 0.5mg/kg sq Q12H*  
  • Apixaban  
  • Heparin 7500 units sq Q12H | CrCl ≥ 30 mL/min  
  • Enoxaparin 0.5mg/kg sq Q12H*  
  • Apixaban  
  • Heparin 7500 units sq Q8H |
| Confirmed VTE or high clinical suspicion TREATMENT | CrCl ≥ 30 mL/min  
  • Enoxaparin 1mg/kg sq Q12H  
  • Apixaban  
  • Therapeutic heparin | CrCl ≥ 30 mL/min  
  • Enoxaparin 1mg/kg sq Q12H  
  • Apixaban  
  • Therapeutic heparin |

## Apixaban Dosing

<table>
<thead>
<tr>
<th>DOAC</th>
<th>D-dimer ≥ 5 mg/L Intermediate Dose Prophylaxis</th>
<th>Confirmed VTE treatment or high clinical suspicion</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>
</tbody>
</table>

*Target anti-Xa levels between 0.3 – 0.7 units/mL  
Consult pharmacy for assistance with dosing recommendations, if needed  
Seek hematology input for further recommendations on treatment as needed, including duration
Appendix 4b: Anticoagulation Dosing Guidelines (Pregnant Patients)

<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></td>
<td></td>
</tr>
</tbody>
</table>
| Prophylaxis      | CrCl ≥ 30 mL/min  
|                  |   - Enoxaparin 40mg sq daily  
|                  | CrCl < 30mL/min  
|                  |   - Enoxaparin 30mg sq daily  |
| ≥ 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*  |
| ≥ 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  |

*Target anti-Xa levels between 0.3 – 0.7 units/mL  
Consult pharmacy for assistance with dosing recommendations, if needed  
Seek hematology input for further recommendations on treatment as needed, including duration
## Appendix 5

### Currently recommended medications for COVID-19

(Subject to change as more data becomes available and based on medication availability)

<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 then reassess | • Prevents acidification of endosomes interrupting cellular functions and replication  
• Prevents viral entry via ACE2 binding  
• Reduction of viral infectivity  
• Immunomodulator | • In-vitro data shows potent SARS-COV-2 inhibition and early clinical data shows possible benefit  
• HCQ was found more potent than chloroquine in inhibiting SARS-CoV-2 in vitro | • QTc prolongation  
• Rash  
• Retinopathy is rare (Baseline eye exam is not required for use for COVID-19) | • There is a theoretical potential for an increase in hydroxychloroquine levels when used with atazanavir therefore monitor for possible QTc prolongation  
• For patients with NG/OG/NT hydroxychloroquine can be crushed for enteral administration  
• Therapy can be extended past 5 days based on patient’s clinical response, but should not exceed 10 total days |

### IMMUNOMODULATING AGENTS

| Tocilizumab¹⁰-¹³ | 8mg/kg IV x 1 dose (actual body weight); dose max 800 mg | • Monoclonal antibody to IL6 receptor | • IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease  
• Retrospective data suggest possible benefit (clinical trials ongoing) | • Headache  
• Elevated liver enzymes  
• Infusion reactions (e.g. flushing, chills) | • The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time  
• Additional doses not indicated at this time |

### Medications which may be available through Clinical Trials

(Subject to change as more data becomes available and based on medication availability)

| Remdesivir¹⁴⁻¹⁷ | **Clinical Trial dosing** | • Viral RNA dependent RNA polymerase inhibitor | • In-vitro data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit | • Nausea, vomiting,  
• Elevated liver enzymes  
• Rectal bleeding  
• As of 3/22/20, remdesivir is available through clinical trials  
• Compassionate use program is available to pregnant patients and those < 18 years of age  
• Gilead will open an expanded access program |
### IMMUNOMODULATING AGENTS

| Sarulimab<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 |

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#### 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>
| Atazanavir<sup>22</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  
• Atazanavir needs an acidic environment for absorption and therefore *antacids, H2 blockers, proton pump inhibitors (PPIs) should be avoided*. If these agents must be given the administration should be separated as below:  
  o Atazanavir should be given 2 hours before or 1 hour after antacids  
  o Atazanavir should be given at the same time as the H2 blocker or the atazanavir should be given 10 hours after or 2 hours before the H2 blocker  
• For PPIs avoid concomitant use |

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*NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir/ritonavir data<sup>19</sup>*
<table>
<thead>
<tr>
<th><strong>Drug</strong></th>
<th><strong>Dosage</strong></th>
<th><strong>Mechanism of Action</strong></th>
<th><strong>Notes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></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>
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<tr>
<td></td>
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<td>• Very limited data on use of azithromycin alone or in combination with other agents         • Gautret, et al. study is limited by small sample size (only 6 patients received HCQ &amp; azithromycin combination) and those patients had lower viral loads than other included patients</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
<td></td>
</tr>
<tr>
<td><strong>Darunavir/Cobicistat</strong></td>
<td>N/A</td>
<td>• Viral protease inhibitor                                                              • In-vitro data shows SARS-COV-2 inhibition</td>
<td>• Decreased binding to viral protease compared to atazanavir. No clinical data at this time</td>
</tr>
</tbody>
</table>
| **Ribavirin**            | N/A        | • Viral RNA polymerase inhibitor and inhibition of elongation of RNA fragments          • *In vitro* data for use in SARS-CoV and MERS-CoV indicates possible activity                                                                 | • Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use  
|                          |            |                                                                                        • Typically used with interferon  
|                          |            |                                                                                        • Studied in patients with other coronaviruses with mixed results                                                      |
| **Oseltamivir**          | N/A        | • Inhibits influenza virus neuraminidase blocking viral release                          • Activity against influenza virus                                                                                                                     | • No current data to support use of this drug.  
|                          |            |                                                                                        • Additionally, *SARS-CoV-2 does not use neuraminidase in the replication cycle* so mechanistically there would be no benefit |
| **Nitazoxanide**         | N/A        | • Augments host antiviral response                                                      • *In-vitro* data reveals SARS-COV-2 inhibition                                                                                                          | • No clinical data available |
### IMMUNOMODULATING AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Route</th>
<th>Key Actions/Interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-beta&lt;sup&gt;30-32&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Immunomodulator</td>
<td>• Possible activity against SARS-CoV and MERS-CoV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Typically used in combination with ribavirin</td>
<td>• Limited data with SARS-CoV-2, toxicity risk outweighs benefit of use</td>
</tr>
<tr>
<td>Corticosteroids&lt;sup&gt;33-37&lt;/sup&gt;</td>
<td></td>
<td>• If indicated per protocol:</td>
<td>Lack of effectiveness and potential harm shown in literature specifically inhibition of viral clearance in severe influenza and SARS&lt;sup&gt;31-34&lt;/sup&gt; though possible benefit with critically ill COVID19 patients&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylprednisolone 40mg q8hr IV for three days, then re-assess</td>
<td>May be considered for use by critical care team for salvage therapy</td>
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<td>• Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression</td>
<td>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</td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG)&lt;sup&gt;38-39&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Neutralizing antibodies against the virus</td>
<td>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</td>
</tr>
<tr>
<td>Baricitinib&lt;sup&gt;40-41&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Janus Kinase (JAK) inhibitor binding cyclin G-associated kinase, may inhibit viral entry via endocytosis</td>
<td>• Not available for off label use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors</td>
<td>No clinical data available</td>
</tr>
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<td></td>
<td></td>
<td>Risk of severe infections with use</td>
</tr>
<tr>
<td>Zinc&lt;sup&gt;42-43&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Directly impairs RNA synthesis in SARS-CoV by inhibiting the replication and transcription complex, as well as RNA-dependent RNA polymerase.</td>
<td>No clinical data is available to demonstrate efficacy in vivo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increasing intracellular zinc concentrations may inhibit RNA synthesis</td>
<td>No in vitro studies have evaluated the effect of zinc on SARS-CoV-2 replication, or hydroxychloroquine as a zinc ionophore</td>
</tr>
<tr>
<td>References:</td>
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<tr>
<td>16) Clinical trials.gov (Identifier NCT04292899 and NCT04292730)</td>
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</tbody>
</table>


24) Clinicaltrials.gov (Identifier NCT04252274)


