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 4/3/20

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)

YES

NO

START TREATMENT (see treatment below)

Supportive Care & Every 4 Hour Oxygen Monitoring
Evaluate for Clinical Trials (YNHH only)

If Oxygen saturation ≤ 93% on room air

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

YES

NO

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

START TREATMENT

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

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

Consider MICU evaluation if > 4 Liter O₂ requirement or hemodynamic instability
(at YNHH see attached 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, and vasculitis.

COVID-SPECIFIC TESTS
1) Baseline & every 12 hours: CRP, Troponin, D-dimer
2) Baseline & every 24 hours: CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
3) Baseline & every 48 hours: Cytokine panel, Angiotensin II level
4) Baseline EKG, and if not on telemetry, daily EKG.
(see appendix 1 for additional 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 3 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 4/3/20**

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 tocolizumab x 1 dose** (in combination with hydroxychloroquine)

If progression in 48 hours despite tocolizumab (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 daily, monitor telemetry** closely for QTc Prolongation
- **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
  - (Appendix 1 for additional recommendations)

**Hematologic:**
- **If D-dimer < 10 mg/L:** All patients should receive **standard prophylactic enoxaparin** unless contraindicated*
  - **If D-dimer ≥10 mg/L:** use **weight-based enoxaparin prophylaxis** 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 confirmed VTE,** start therapeutic dose anticoagulation unless contraindicated*
  - **If signs of nasal or digital ischemia OR ferritin >100,000,** consider Hematology consult at discretion of primary team
  - *(see appendix 3 for dosing recommendations)*

**COVID-SPECIFIC TESTS**

1) **Baseline & every 12 hours:** CRP, Troponin, D-dimer
2) **Baseline & every 24 hours:** CBC with differential, CMP, Ferritin, Procalcitonin, BNP, fibrinogen, PT/PTT, Mg
3) **Baseline & every 48 hours:** Cytokine panel, Angiotensin II level
4) **Baseline EKG,** and if not on telemetry, **daily EKG.** *(see appendix 1 for additional recommendations)*
5) **Repeat Chest X-Ray:** if clinical deterioration.

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
## 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>
| Hydroxy-chloroquine (HCQ)\(^1\-^9\) | 400mg PO q12h x 24h followed by 200mg q12h x 4 days for a 5 day total duration then re-assess | • Prevents acidification of endosomes interrupting cellular functions and replication  
• Prevents viral entry via ACE2 binding  
• Reduction of viral infectivity  
• Immunomodulator | • In-vitro data shows potent SARS-COV-2 inhibition and early clinical data shows possible benefit  
• HCQ was found more potent than chloroquine in inhibiting SARS-CoV-2 in vitro | • QTc prolongation  
• Rash  
• Retinopathy is rare *(Baseline eye exam is not required for use for COVID-19)* | • There is a theoretical potential for an increase in hydroxychloroquine levels when used with atazanavir therefore *monitor for possible QTc prolongation*  
• For patients with NG/OG/NT hydroxychloroquine can be crushed for enteral administration  
• Therapy can be extended past 5 days based on patient’s clinical response, but should not exceed 10 total days |

### IMMUNOMODULATING AGENTS

| Tocilizumab\(^10\-^13\) | 8mg/kg IV x 1 dose (actual body weight); dose max 800 mg | • Monoclonal antibody to IL6 receptor | • IL-6 receptor antagonist may attenuate cytokine release in patients with severe disease  
• Retrospective data suggest possible benefit *(clinical trials ongoing)* | • Headache  
• Elevated liver enzymes  
• Infusion reactions *(e.g. flushing, chills)* | • The use of IL-6 levels should NOT guide decision to administer tocilizumab at this time  
• Additional doses not indicated at this time |

## Medications which may be available through Clinical Trials

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

| Remdesivir\(^14\-^16\) | **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 only and not through compassionate use except for pregnant patients and those < 18 years of age still have the option for compassionate use program  
• Gilead is working on an expanded access program |
**IMMUNOMODULATING AGENTS**

| Sarulimab<sup>17, 19</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, 20&lt;/sup&gt;</td>
<td>400mg/100 mg PO q24h x 5 days then reassess</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>Atazanavir&lt;sup&gt;21&lt;/sup&gt;</td>
<td>400mg (2-200mg caps) PO q24h x 5 days then re-assess</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></td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Mechanism</td>
<td>Comments</td>
<td></td>
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</table>
| Azithromycin             | 500 mg x 1, followed by 250 mg q24h x 4 days | Not well defined; possible immunomodulator  
In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load |  
- Very limited data on use of azithromycin alone or in combination with other agents  
  - Gautret, et al. study is limited by small sample size (only 6 patients received HCQ & azithromycin combination) and those patients had lower viral loads than other included patients  
  - Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation |  |
| Darunavir/Cobicistat     | 800 mg/150 mg PO q24h x 5 days              | Viral protease inhibitor  
In-vitro data shows SARS-CoV-2 inhibition |  
- Decreased binding to viral protease compared to atazanavir. No clinical data at this time |  |
| Ribavirin                | 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 |  |
| Oselamivir               | 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>N/A</th>
<th>Role</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon-beta</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>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Have been studied for patients with other coronaviruses with mixed results</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Not interferon-alpha or interferon-gamma</td>
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<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td>• Inhibit production of inflammatory cytokines that regulate neutrophil and T-cell responses leading to immune suppression</td>
<td>• 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</td>
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<td></td>
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<td></td>
<td>• May be helpful in attenuating cytokine release in patients with severe disease</td>
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<td></td>
<td></td>
<td></td>
<td>• May be considered for use by critical care team for salvage therapy</td>
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<td></td>
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<td></td>
<td>• <strong>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</strong></td>
</tr>
<tr>
<td>Intravenous</td>
<td>N/A</td>
<td>• Neutralizing antibodies against the virus</td>
<td>• May have both antiviral and immunomodulatory effects</td>
</tr>
<tr>
<td>Immunoglobulin (IVIG)</td>
<td></td>
<td></td>
<td>• A recent observational study reported clinical and radiographic improvement in 3 patients who received high dose IVIG at time of respiratory distress</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>• Drug is on <strong>critical national shortage</strong> and has an unclear role as current preparations will not contain antibodies against SARS-CoV-2 at this time</td>
</tr>
<tr>
<td>Baricitinib</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></td>
<td>• No clinical data available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Risk of severe infections with use</td>
</tr>
</tbody>
</table>

**References:**

16) Clinical trials.gov (Identifier NCT04292899 and NCT04292730).
23) Clinicaltrials.gov (Identifier NCT04252274)
**Appendix 1: 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.

<table>
<thead>
<tr>
<th>In all COVID-19 patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>•</strong> Eliminate any unnecessary medication that may prolong the QT interval</td>
</tr>
<tr>
<td><strong>•</strong> Keep K&gt; 4.0 and Mg&gt;2.0</td>
</tr>
</tbody>
</table>

### Baseline ECG (at admission or within 30 days)

<table>
<thead>
<tr>
<th>QTC &lt; 470 ms, narrow QRS or QTC &lt; 500ms, wide QRS (&gt;120 ms)</th>
<th>QTC &gt; 470 ms, narrow QRS or QTC &gt; 500 ms, wide QRS (&gt;120 ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telemetry <strong>not</strong> routinely required for QTc monitoring*</td>
<td>Admit to telemetry</td>
</tr>
<tr>
<td>Check ECG 2 hrs after 2nd dose</td>
<td>No Telemetry Available</td>
</tr>
<tr>
<td>No Change in QTc interval</td>
<td>Check QTc on telemetry 2 hrs after morning dose</td>
</tr>
<tr>
<td>QTC increase &gt; 50 ms Or absolute QTC &gt; 500 ms</td>
<td>Discuss risk/benefit of therapy with Clinical Pharmacy, ID and EP services</td>
</tr>
<tr>
<td>Check daily ECG 2 hrs after morning dose</td>
<td>QTc increase &gt; 50 ms</td>
</tr>
<tr>
<td>&gt;Confirm QTc prolongation with EP service</td>
<td>Verify by 12-lead ECG</td>
</tr>
<tr>
<td>&gt;Move to telemetry</td>
<td>&gt;Confirms QTc prolongation with EP service</td>
</tr>
<tr>
<td>&gt;Discuss with clinical pharmacy, ID and EP services</td>
<td>&gt; Discuss with clinical pharmacy, ID and EP services</td>
</tr>
</tbody>
</table>

* Telemetry may be considered for other clinical reason

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For extreme baseline QTc prolongation
QTC > 500 ms narrow QRS
QTC > 550 wide QRS
Discuss risk/benefit of therapy with EP and ID services
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

- >4L NC with O2 sat

- RR > 25 +/- AMS +/- inability to manage secretions
  - Obtain ABG and consult

- pH > 7.32
  - Consult
Appendix 3: Enoxaparin Dosing Guidelines:

All COVID-19 patients should receive VTE prophylaxis with enoxaparin unless contraindicated. If D-dimer > 10 mg/L and critically ill, increase to intermediate-dose weight-based VTE prophylaxis. If confirmed VTE, begin therapeutic enoxaparin unless contraindicated.

1) VTE prophylaxis in patients with D-dimer < 10 mg/L
   - **CrCl ≥ 30 mL/min**
     - BMI < 40 kg/m²
       - Enoxaparin injection 40 mg sq daily
     - BMI ≥ 40 kg/m²
       - Enoxaparin injection 40 mg sq Q12H
   - **CrCl < 30 mL/min**: Consult pharmacy and/or hematology for recommendations on enoxaparin dosing with anti-Xa level monitoring

2) If D-dimer ≥ 10 mg/L, increase to intermediate-dose weight-based VTE prophylaxis
   - Enoxaparin 0.5 mg/kg sq Q12H
   - **CrCl < 30 mL/min**: Consult pharmacy and/or hematology for enoxaparin with anti-Xa level monitoring

3) VTE Treatment- Confirmed VTE or high clinical suspicion for VTE
   - Enoxaparin 1 mg/kg sq Q12H
   - **CrCl < 30 mL/min**: Consult pharmacy and/or hematology for enoxaparin with anti-Xa level monitoring.