**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 3/31/20

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

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

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

**START TREATMENT (see treatment below)**

**B-Presence of:**
1) **Fever** and/or **signs & symptoms of respiratory disease** *(e.g. cough, dyspnea)*
   - OR
2) **Chest imaging** showing pulmonary infiltrates

**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*

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
</table>

**START TREATMENT**

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

If ≥ 3 Liter O₂ requirement
- OR any supplemental O₂ requirement & **hs-CRP >70**
- Consider **tocilizumab**
- Inform MICU and proceed to Severe algorithm

**COVID-SPECIFIC TESTS**
1) **Draw at Baseline & every 12 hours:**
   - CRP, CBC with differential, Ferritin, Procalcitonin, LDH, BNP, troponin, D-dimer, fibrinogen, PT/PTT
2) **Draw at Baseline Only:**
   - HIV-1/HIV-2 antibody/antigen.
3) **Draw at baseline & every 48 hours:**
   - Cytokine panel
4) **Baseline EKG, and if not on telemetry, daily EKG. (Appendix for addt’l recommendations)**
5) **Repeat Chest X-Ray** if clinical deterioration

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

**Cardiac:** If troponin or BNP is abnormal, or new EKG changes, obtain TTE and consult cardiology

**Hematologic:** Give all patients weight-based prophylactic anticoagulation with enoxaparin unless contraindicated

---

*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.

Algorithm reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
YNHHS Initial Treatment Algorithm for **Hospitalized** PATIENTS 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 3/31/20

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**
(in combination with hydroxychloroquine)

**If progression in 48 hours despite tocilizumab**
(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

**Cardiac:**
- **Monitor electrolytes:** **Replete Mg >2, K >4**
- **Baseline EKG daily, monitor telemetry**
closely for QTc Prolongation
- **Caution combining QTc prolonging medications**
- If troponin or BNP are abnormal, or new EKG changes, obtain TTE and consult cardiology
(Appendix for additional recommendations)

**Hematologic:**
- **All patients:** give prophylactic weight-based anticoagulation with enoxaparin unless contraindicated
- **If signs of nasal or digital ischemia OR ferritin >100,000** consider Hematology consult at discretion of primary team
- **If D-dimer >10mg/L and critically ill,** assess for presence of VTE and consider Hematology input. If confirmed VTE, begin therapeutic enoxaparin unless contraindicated.

**COVID-SPECIFIC TESTS**

1) **Draw at Baseline & every 12 hours:**
CRP, CBC with differential,
Procalcitonin, Ferritin, LDH, BNP
troponin, D-dimer, fibrinogen, PT/PTT

2) **Draw at Baseline Only:**
HIV-1/HIV-2 antibody/antigen

3) **Draw at baseline & every 48 hours:**
Cytokine panel

4) **Repeat CXR** if clinical deterioration

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

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>
| Hydroxychloroquine (HCQ) | 400mg PO q12h x 24h 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
• Reduces 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

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

Medications which may be available through Clinical Trials
(Subject to change as more data becomes available and based on medication availability)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Trial dosing</th>
<th>Rationale for use</th>
<th>Notable Adverse Reactions</th>
<th>Other considerations</th>
</tr>
</thead>
</table>
| Remdesivir              | Clinical Trial dosing | • Viral RNA dependent RNA polymerase inhibitor
• In-vitro data reveals potent SARS-COV-2 inhibition and early clinical data shows possible benefit | • Nausea, vomiting, Elevated liver enzymes
• Rectal bleeding | • As of 3/22/20 remdesivir is available through clinical trials 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**

- **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</td>
<td>400mg/100mg 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</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>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</td>
</tr>
</tbody>
</table>

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**Note:**

- 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>Dosage</th>
<th>Mechanisms</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</td>
<td>• In a small study, combination of HCQ and azithromycin was associated with significant a reduction in SARS-CoV-2 viral load</td>
</tr>
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<td></td>
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<td>• Very limited data on use of azithromycin alone or in combination with other agents</td>
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<tr>
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<td></td>
<td>o Gautret, et al. study is limited by small sample size (only 6 patients received HCQ &amp; azithromycin combination) and those patients had lower viral loads than other included patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
</tr>
<tr>
<td>Darunavir/Cobicistat</td>
<td>800 mg /150 mg PO q24h x 5 days</td>
<td>• Viral protease inhibitor</td>
<td>• In-vitro data shows SARS-COV-2 inhibition</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</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>
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<tr>
<td></td>
<td></td>
<td></td>
<td>o 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</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>
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<td></td>
<td>o Additionally, <strong>SARS-CoV-2 does not use neuraminidase in the replication cycle</strong> 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></td>
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<td></td>
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<tr>
<td>--------------------------</td>
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<tr>
<td><strong>Interferon-beta</strong> 28-30</td>
<td>N/A</td>
<td>- Immunomodulator</td>
<td>- Possible activity against SARS-CoV and MERS-CoV&lt;br&gt;Typically used in combination with ribavirin</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong> 31-35</td>
<td>If indicated per algorithm: 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&lt;br&gt;- May be helpful in attenuating cytokine release in patients with severe disease</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&lt;br&gt;May be considered for use by critical care team for salvage therapy&lt;br&gt;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><strong>Intravenous immunoglobulin (IVIG)</strong> 36-37</td>
<td>N/A</td>
<td>- Neutralizing antibodies against the virus&lt;br&gt;- May have both antiviral and immunomodulatory effects&lt;br&gt;- A recent observational study reported clinical and radiographic improvement in 3 patients who received high dose IVIG at time of respiratory distress</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><strong>Baricitinib</strong> 38-39</td>
<td>N/A</td>
<td>- Janus Kinase (JAK) inhibitor binding cyclin G-associated kinase, may inhibit viral entry via endocytosis&lt;br&gt;- May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors</td>
<td>- Not available for off label use&lt;br&gt;No clinical data available&lt;br&gt;Risk of severe infections with use</td>
</tr>
</tbody>
</table>

References:
15) Clinical trials.gov (Identifier NCT04292899 and NCT04292730).
22) 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.