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

---

**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)

**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

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

**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)

---

*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 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 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 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 ≥10mg/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.

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 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                   | 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                   | 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\(^{17,19}\) | 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(^{8,20})</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>
</tbody>
</table>
| Atazanavir\(^{21}\)     | 400mg (2-200mg caps) PO q24h x 5 days then re-assess | Viral protease inhibitor                       | More potent binding to the virus compared to other protease inhibitors *in vitro* (lower than lopinavir) | 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:  
  - Atazanavir should be given 2 hours before or 1 hour after antacids  
  - 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 |

### Updated Lopinavir/ritonavir data \(^{19}\)
**NO LONGER RECOMMENDED AS FIRST LINE due to updated Lopinavir/ritonavir data**

- Drug should be given at the same time as the H2 blocker or the lopinavir/ritonavir should be given 10 hours after or 2 hours before the H2 blocker.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Usage</th>
<th>Mechanism/Activity</th>
<th>Notes/Warnings</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>• In a small study, combination of HCQ and azithromycin was associated with significant reduction in SARS-CoV-2 viral load</td>
<td>• Very limited data on use of azithromycin alone or in combination with other agents</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>• Very limited data on use of azithromycin alone or in combination with other agents</td>
<td>• Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
</tr>
<tr>
<td>Darunavir/</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>Cobicistat</td>
<td></td>
<td>• Viral protease inhibitor</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>• In-vitro data for use in SARS-CoV and MERS-CoV indicates possible activity</td>
<td>• Limited evidence for SARS-CoV-2 and toxicity risk outweighs benefit of use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In-vitro data for use in SARS-CoV and MERS-CoV indicates possible activity</td>
<td>• Typically used with interferon</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• In-vitro data for use in SARS-CoV and MERS-CoV indicates possible activity</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>• In-vitro data reveals SARS-COV-2 inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Activity against influenza virus</td>
<td>• No current data to support use of this drug.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Activity against influenza virus</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></td>
<td></td>
<td>• In-vitro data reveals SARS-COV-2 inhibition</td>
<td></td>
</tr>
</tbody>
</table>
## IMMUNOMODULATING AGENTS

<table>
<thead>
<tr>
<th>Interferon-beta$^{29-31}$</th>
<th>N/A</th>
<th>Immunomodulator</th>
<th>Possible activity against SARS-CoV and MERS-CoV</th>
<th>Typically used in combination with ribavirin</th>
<th>Limited data with SARS-CoV-2, toxicity risk outweighs benefit of use</th>
<th>Have been studied for patients with other coronaviruses with mixed results</th>
<th>Not interferon-alpha or interferon-gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids$^{32-36}$</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>
<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>
<td>May be considered for use by critical care team for salvage therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous immunoglobulin (IVIG)$^{37-38}$</td>
<td>N/A</td>
<td>Neutralizing antibodies against the virus</td>
<td>May have both antiviral and immunomodulatory effects</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>
<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>
<td></td>
<td></td>
</tr>
<tr>
<td>Baricitinib$^{39-40}$</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>
<td>Not available for off label use</td>
<td>No clinical data available</td>
<td>Risk of severe infections with use</td>
<td></td>
</tr>
</tbody>
</table>

References:


Clinical trials.gov (Identifier NCT04292899 and NCT04292730).


Tomonori Ishii ea. 2019. Pharmacodynamic effect and safety of single-dose sarilumab SC or tocilizumab IV or SC in patients with rheumatoid arthritis. Annual Meeting of the American College of Rheumatology. Bethesda, MD, USA.

Clinical Study Protocol 6R88-COV-2040 Original Regeneron Pharmaceuticals, Inc. Page 78


Clinical trials.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.

---

**In all COVID-19 patients:**
- Eliminate any unnecessary medication that may prolong the QT interval
- Keep K> 4.0 and Mg>2.0

---

**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><strong>Telemetry not routinely required for QTC monitoring</strong></td>
<td><strong>Admit to telemetry</strong></td>
</tr>
<tr>
<td><strong>Check ECG 2 hrs after 2nd dose</strong></td>
<td><strong>No Telemetry Available</strong></td>
</tr>
<tr>
<td><strong>No Change in QTC interval</strong></td>
<td><strong>Check QTC on telemetry 2 hrs after morning dose</strong></td>
</tr>
<tr>
<td><strong>QTC increase &gt; 50 ms or absolute QTC &gt; 500 ms</strong></td>
<td><strong>QTC increase &gt; 50 ms</strong></td>
</tr>
<tr>
<td><strong>Check daily ECG 2 hrs after morning dose</strong></td>
<td><strong>Verify by 12-lead ECG</strong></td>
</tr>
<tr>
<td>&gt;Confirm QTC prolongation with EP service &gt;Move to telemetry &gt;Discuss with clinical pharmacy, ID and EP services</td>
<td>&gt;Confirm QTC prolongation with EP service &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:

- >4L NC with O2 sat
  - RR < 25
    - Obtain ABG
      - pH > 7.32
        - Consider SDU evaluation, reassess in 2-4 hours
      - Hypercapnia with pH < 7.32
        - Consult
  - Hypercapnia with pH < 7.32
    - Consult
  - RR > 25 +/- AMS +/- inability to manage secretions
    - Obtain ABG and consult

- pH > 7.32
  - RR > 25 +/- AMS +/- inability to manage secretions
    - Obtain ABG and 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.