YNHHS Treatment Algorithm for Hospitalized PATIENT 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.

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

Presence of:
Oxygen saturation ≤ 93% on room air OR on chronic O₂ supplementation

YES

START TREATMENT (see treatment below)

If Oxygen saturation ≤ 93%

SUPPORTIVE CARE & CLOSE OBSERVATION with Continuous/ frequent O₂ Sat monitoring

NO

Presence of:
1) Fever and/or signs & symptoms of respiratory disease (e.g. cough, dyspnea) AND
2) Chest imaging showing bilateral infiltrates

YES

Does patient have:
Age ≥ 60 OR Morbid Obesity with BMI ≥ 40 OR Chronic heart disease OR Chronic lung disease OR Immunosuppressed state

NO

YES

START TREATMENT

TREATMENT
1) atazanavir¹,² AND hydroxychloroquine¹,²

2) Consult to Inpatient ID Required
ID will determine eligibility for remdesivir clinical trial (Currently only available at YNHH)

At YNHH: From 8AM - 5PM: Place EPIC Order for ID Consult
From 5PM to 8AM: call on-call ID fellow

At BH, GH, LMH/WH: follow the normal process for ID consult

3) If > 3 Liter O₂ requirement, consider starting tocilizumab¹,², inform MICU and ID, and proceed to the Severe algorithm

COVID-SPECIFIC TESTS
1) Draw at Baseline & every 12 hours:
CRP, 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) Baseline EKG & daily EKG if not on telemetry

Algorithm Updated as of 3/23/20 reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team

¹Restricted medication requires ID and/or non-formulary approval. Pharmacist to review possible drug-drug interactions.
²Limited data

*If mechanically ventilated or on ECMO, proceed to Severe algorithm

*(If mechanically ventilated or on ECMO, proceed to Severe algorithm)
YNHHS 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.

**Respiratory failure with Mechanical ventilation (including ECMO) PLUS confirmed POSITIVE SARS-CoV-2 by PCR**

**TREATMENT**

*atazanavir*[^1],[^2] & *hydroxychloroquine*[^1],[^2]

Consult Inpatient Infectious Diseases to consider other therapies

**At YNHH:** From 8AM - 5PM: Place EPIC Order for ID Consult
From 5PM to 8AM: call on-call ID fellow
**At BH, GH, LMH/WH:** follow the normal process for ID consult

Consider *tocilizumab* x 1 dose

(Additional doses determined by clinical response given the drug’s long half-life in consultation with ID, pharmacy, & critical care)

**COVID-SPECIFIC TESTS**

1) **Draw at Baseline & every 12 hours:**
   - CRP, 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) **Baseline EKG & daily EKG if not on telemetry**

**Remdesivir** is no longer available for compassionate use. Gilead is transitioning to a clinical trial and extended access program which is actively being pursued. Cases will be reviewed for clinical trial candidacy.

Monitor patients closely for *digital and nasal tip ischemia*

Monitor electrolytes:
   - *Replete Mg >2, K >4*
Follow EKG/Telemetry closely for QTc Prolongation

Caution combining QTc prolonging medications

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[^1]: Restricted medication requires ID and/or non-formulary approval. Pharmacist to review possible drug-drug interactions
[^2]: Limited data

Algorithm Updated as of 3/24/20 reviewed by YNHHS SAS and YNHH/YSM Ad-Hoc COVID-19 Treatment Team
<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>
| **Atazanavir**<sup>1</sup> | 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:  
  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  
  o For PPIs avoid concomitant use |  
| **Hydroxychloroquine (HCQ)**<sup>2-10</sup> | 400mg PO q12h x 24h followed by 200mg q12h x 5 days then re-assess | • Prevents acidification of endosomes interrupting cellular functions and replication  
• Prevents viral entry via hACE2 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 |  |
| **Remdesivir**<sup>11-13</sup> | 200 mg IV x1, then 100 mg IV q24h, up to 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  
• As of 3/22/20 Gilead 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 |  |
| **Tocilizumab**<sup>14-17</sup> | 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  
• 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 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>400mg/100 mg PO q24h x 5 days then</td>
<td>• Viral protease inhibitor</td>
<td>• In-vitro data reveals potent SARS-CoV-2 inhibition and early clinical data reveals possible</td>
<td>• Limited availability, poor tolerability (GI side effects and recent data demonstrated questionable clinical</td>
</tr>
<tr>
<td>ritonavir&lt;sup&gt;9,18&lt;/sup&gt;</td>
<td>reassess</td>
<td></td>
<td>benefit in mild-moderate cases if given early in course of disease</td>
<td>efficacy</td>
</tr>
<tr>
<td>Azithromycin&lt;sup&gt;10&lt;/sup&gt;</td>
<td>500 mg x 1, followed by 250 mg q24h x 4</td>
<td>• Not well defined; possible immunomodulator</td>
<td>• In a small study, combination of HCQ and azithromycin was associated with significant a</td>
<td>• Very limited data on use of azithromycin alone or in combination with other agents</td>
</tr>
<tr>
<td>Darunavir/</td>
<td>800 mg /150 mg PO q24h x 5 days</td>
<td>• Viral protease inhibitor</td>
<td>reduction in SARS-CoV-2 viral load</td>
<td>○ Gautret et al. study is limited by small sample size (only 6 patients received HCQ &amp; azithromycin</td>
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<tr>
<td>cobicistat&lt;sup&gt;19&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td>combination) and those patients lower viral loads than other included patients</td>
</tr>
<tr>
<td>Ribavirin&lt;sup&gt;20-22&lt;/sup&gt;</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>
<td>• Combination of HCQ and azithromycin and atazanavir can increase the risk for QTc prolongation</td>
</tr>
<tr>
<td>Osel tamivir&lt;sup&gt;23&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Inhibits influenza virus neuraminidase</td>
<td>Activity against influenza virus</td>
<td></td>
</tr>
<tr>
<td>Nitazoxanide&lt;sup&gt;24&lt;/sup&gt;</td>
<td>N/A</td>
<td>• Targets host-regulated processes involved in viral replication</td>
<td>• In-vitro data reveals SARS-CoV-2 inhibition</td>
<td>• No clinical data available</td>
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<tr>
<th><strong>IMMUNOMODULATING AGENTS</strong></th>
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<tr>
<td><strong>Interferon-beta</strong>&lt;sup&gt;22-27&lt;/sup&gt;</td>
<td>N/A</td>
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<tr>
<td>• Immunomodulator</td>
<td>• Possible activity against SARS-CoV and MERS-CoV and typically used in combination with ribavirin</td>
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<tr>
<td><strong>Corticosteroids</strong>&lt;sup&gt;28-32&lt;/sup&gt;</td>
<td>Not well defined</td>
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<tr>
<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>
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<tr>
<td><strong>Intravenous immunoglobulin (IVIG)</strong>&lt;sup&gt;33-34&lt;/sup&gt;</td>
<td>N/A</td>
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<td>• Neutralizing antibodies against the virus</td>
<td>• May have both antiviral and immunomodulatory effects</td>
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<td>• A recent observational study reported clinical and radiographic improvement in 3 patients who received high dose IVIG at time of respiratory distress</td>
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<tr>
<td><strong>Baricitinib</strong>&lt;sup&gt;35-36&lt;/sup&gt;</td>
<td>N/A</td>
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<td>• Janus Kinase Inhibitor (JAK) that binds cyclin G-associated kinase, a regulator of endocytosis; hence, inhibits viral entry</td>
<td>• May have targeted antiviral and immunomodulatory effect with less side-effects at an effective dose than other JAK inhibitors</td>
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References: