Suggested Management of Hospitalized COVID-19 Patients - March 31, 2020 1600

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*highlighted information denotes new content

**Purpose**

- The purpose of this document is to provide guidance for the management of patients with laboratory confirmed novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, aka COVID-19, until further information becomes available from the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO).

- Given the rapidly evolving nature of data on COVID-19, this document is living document that will be updated in real time.
  - Spectrum Health is currently in the process of enrolling in clinical trials for the treatment of COVID-19. The information below is subject to change as our institutions gain access to this ongoing research. Please contact Dr. Gordana Simeunovic, MD – SHMG Adult Infectious Diseases with any questions regarding clinical trials for COVID-19.

- This document was developed by members of the ID division at Spectrum Health in conjunction with pharmacy, immunology, ICU and other medicine divisions to provide guidance to frontline clinicians caring for patients with COVID-19.

- The options listed below are NOT licensed for the treatment of COVID-19, they include potential off-label and/or experimental use of medications. They should NOT be considered as curative for COVID-19 and clinical judgment should be used when weighing the benefits of these unproven treatment options versus the risks of adverse effects.

- This document also provides a guideline for the work up for all patients hospitalized for confirmed COVID-19. It does NOT cover recommendations for infection control, PPE, management of complications in patients with COVID-19.
Figure 1 – Suggestive Management of Hospitalized Patients with Confirmed COVID-19

**NOTE:** Systemic corticosteroids should be avoided in the treatment of COVID-19. Inhaled corticosteroids should be discontinued if possible. See the last page of this guideline for more information.

Hospitalized patient with confirmed COVID-19

Baseline Orders – [See Table 1]

Non-ICU Admission

Perform Risk Stratification
[See Table 2]

High Risk

**NOTE:** For special populations – [See Table 4]

No need to repeat daily labs in [Table 1]. If clinically worsening, treat as high risk

Non-High Risk

No pharmacologic treatment indicated, continue close monitoring & supportive care

Repeated daily labs – [See Table 1]

Immunocompromised OR Pre-existing lung disease

**Consider** Hydroxychloroquine*

Treatment Pearls - [See Table 3]

Immunology will follow daily labs to help guide ordering of tocilizumab or anakinra

Immunology will contact the attending physician to discuss and order appropriate agent

NOTE: Concomitant bacterial pneumonia appears to be rare in patients with confirmed COVID-19. Re-evaluate need for antibiotic therapy daily.

There is insufficient evidence to support the routine addition of azithromycin to hydroxychloroquine for the experimental treatment of COVID-19.

Pediatric Admission (< 18 years)

Consult Pediatric ID to discuss hydroxychloroquine initiation

*If hydroxychloroquine unavailable or contraindicated, consider chloroquine, lopinavir/ritonavir, or compassionate use remdesivir in case by case basis

Alternatives outlined below

Pediatric Admission (< 18 years)

Hospitalized patient with confirmed COVID-19

Baseline Orders – [See Table 1]

Non-ICU Admission

Perform Risk Stratification
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**NOTE:** Routine ID consultation is not required for mild-moderate cases. If lack of clinical improvement, consider ID consultation.

All cases of COVID-19 treated with pharmacologic therapy will be reviewed by SH Adult & Pediatric Antimicrobial Stewardship Program for appropriateness.
Table 1 – Spectrum Health Recommended COVID-19 Laboratory Monitoring

The labs labeled below will be evaluated by SHMG Allergy & Immunology peripherally to assess for initiation of immunomodulating therapy. **These laboratory values are non-specific markers of inflammation. They are non-diagnostic for COVID-19 and would be expected to be elevated in patients with significant inflammatory process.**

Once COVID-19 ruled out and severe respiratory isolation discontinued, please discontinue these daily labs. Contact Dr. Nicholas Hartog directly with questions.

All labs should be ordered daily “qAM” to limit blood draws and exposure:

- CMP
- CBC with differential
- CRP
- Ferritin
- Fibrinogen
- D-dimer
- LDH
- Triglycerides

To be reviewed daily by SHMG Allergy & Immunology

To be ordered for suspected or proven COVID-19 adults, but not daily unless otherwise indicated:

- Blood Cultures
- Chest x-ray
- Consider CPK to assess for rhabdomyolysis in light of elevated TG with use of Propofol

**NOTE:** CT scans are not diagnostic for COVID-19, and should be ordered only if results will change patient management.

Table 2 - Spectrum Health COVID-19 Risk Stratification

*High Risk = Any patient with at least one criteria from each column OR multiple clinical criteria*

<table>
<thead>
<tr>
<th>History</th>
<th>Clinical Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 60 years</td>
<td>O2 saturation &lt; 90% on room air or baseline O2</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>D-dimer &gt; 1000 ng/mL</td>
</tr>
<tr>
<td>ESRD</td>
<td>LDH &gt; 245 U/L</td>
</tr>
<tr>
<td>Diabetes (A1C ≥ 7.6)</td>
<td>CRP &gt; 20 mg/L</td>
</tr>
<tr>
<td></td>
<td>Absolute lymphocytes &lt; 0.8</td>
</tr>
</tbody>
</table>

Table 3 - Spectrum Health COVID-19 Treatment Pearls

1. All adult patients with COVID-19 should receive DVT prophylaxis. Pediatric patients ≥ 12 years with COVID-19 should be evaluated to receive DVT prophylaxis.
2. In the setting of ARDS, BiPAP is unlikely to be useful. Consider intubation early in COVID positive patients with worsening respiratory failure.
3. Consider echo or cardiac markers if there is cardiac dysrhythmia or hemodynamic decline in the course of care as some cohorts have suggested late cardiomyopathy.
4. Low tidal volume vent and high PEEP (data suggests lots of patients have diffuse GGO but higher compliance)
5. Many COVID patients benefit from proning, and may benefit from long periods of proning (18 -22 hours).
### Table 4 – Treatment of COVID-19 in Special Populations

<table>
<thead>
<tr>
<th>Category</th>
<th>Recommendation</th>
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| **Cardiovascular Disease**      | • *Statins* - Patients with a history of cardiovascular disease that are hospitalized with COVID-19 may benefit from being on statin therapy. For patients already on statin therapy, continue this treatment while they are hospitalized with consideration given to monitoring for rhabdomyolysis.  
  o Patients without a cardiovascular indication for statin therapy should **not** be started on a statin for the treatment of COVID-19.  
  • *ACE Inhibitors/ARBs* - There are no clear data to suggest harm nor benefit of therapy with ACE inhibitors or ARBs in the treatment of COVID-19. Patients already receiving these medications should continue them as prescribed; even during a hospitalization for COVID-19. These medications should not be started unless otherwise indicated. |
| **Chronic Lung Disease**         | • Patients with a history of chronic lung disease may benefit from the anti-inflammatory effects of azithromycin when given in addition to hydroxychloroquine for the treatment of COVID-19.  
  o Patients treated with hydroxychloroquine and azithromycin should be monitored for QTc prolongation |
| **Pregnancy**                    | • General principles for management of COVID-19 during pregnancy include early isolation, aggressive infection control measures, rapid testing for co-infections, oxygen therapy as needed, fetal and uterine contraction monitoring, early mechanical ventilation for progressive respiratory failure, individualized delivery planning, and a multi-specialty team-based approach.  
  • For hospitalized patients, consider pulmonary OR infectious disease consult under which guidance the following options could be considered:  
  o Lopinavir/ritonavir x 10 days  
  o Hydroxychloroquine x 5 days  
  • Decisions about the use of corticosteroids for fetal lung maturity should be made in consultation with ID specialists and maternal-fetal medicine consultants |
<p>| <strong>Children &lt; 18 years</strong>          | • Pediatric Infectious Diseases Consultation Recommended |
| <strong>Immunocompromised Patients</strong>   | • Begin treatment with hydroxychloroquine or alternative therapy as indicated. Infectious Diseases consultation is recommended for all solid organ and bone marrow transplant patients |
| <strong>Post-Exposure Prophylaxis</strong>    | • CDC does <strong>NOT</strong> endorse post-exposure prophylaxis for people who may have been exposed to COVID-19 at this time |</p>
<table>
<thead>
<tr>
<th>Therapeutic Agent &amp; Mechanism</th>
<th>Data on Use</th>
<th>Dosing Strategies</th>
<th>Duration of Therapy</th>
<th>Renal Dosing</th>
<th>Monitoring/Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydroxychloroquine:</strong> Blocks acidification of endosome, lysosome, Golgi; blocks fusion and possibly uncoating</td>
<td>More potent at inhibiting SARS-Co-V-2 than chloroquine in vitro(^1)</td>
<td><strong>Neonatal</strong>&lt;br&gt;6.5 mg/kg per dose PO twice daily for 2 doses on day 1 (maximum 400 mg per dose), followed by 3.5 mg/kg per dose PO twice daily for 8 doses on days 2-5 (maximum 200 mg per dose)&lt;br&gt;&lt;br&gt;<strong>Pediatric</strong>&lt;br&gt;400 mg PO twice daily for 2 doses on day 1, followed by 200 mg PO twice daily for 8 doses on days 2-5</td>
<td>5 days.&lt;br&gt;In select patients with extended ventilation or profound immunosuppression duration may be extended</td>
<td>No renal or hepatic adjustments necessary</td>
<td>May be used in pregnancy&lt;br&gt;Extemporaneously prepared suspension (25 mg/mL) available for enteral tube administration.&lt;br&gt;Major Adverse Events:&lt;br&gt;• GI intolerance&lt;br&gt;• QTc prolongation&lt;br&gt;• Hypoglycemia&lt;br&gt;Consider monitoring for QTc prolongation; especially when using with other QTC prolonging medications&lt;br&gt;No need for G6PD deficiency screening prior to therapy</td>
</tr>
</tbody>
</table>

\(^1\) Yao X et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Co-V-2).
<table>
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<tr>
<th><strong>Chloroquine</strong></th>
<th>Reduced hospital stay and progression on pneumonia(^2) in uncontrolled study</th>
<th>Neonatal Pediatric 8.3 mg/kg per dose PO twice daily (maximum 500 mg per dose)</th>
<th>5 days. In select patients with extended ventilation or profound immunosuppression duration may be extended</th>
<th>Adult: GFR &lt; 10mL/min OR HD: 250mg (150mg base) twice daily CRRT: No dose adjustments</th>
<th>May be used in pregnancy Extemporaneously prepared suspension (15mg/mL =9mg/mL BASE) may be administered via enteral tubes with satisfactory absorption Major Adverse Events: • GI intolerance • QTc prolongation Consider monitoring for QTc prolongation; especially when using with other QTc prolonging medications</th>
</tr>
</thead>
</table>


\(^3\) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. DOI: https://doi.org/10.1038/s41422-020-0282-0

\(^4\) Yao X et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory
| **Lopinavir/Ritonavir (Kaletra):** Inhibits viral protease which is necessary for viral cleavage (which is necessary for replication) | Hasn’t been found to be effective with early clinical data. Small reports suggesting early use in patients with ARDS may provide some benefit. | Pediatric dosing regimens based on lopinavir component

**Neonatal**
Lopinavir 300 mg/m² per dose PO twice daily (or 16 mg/kg per dose)

**Pediatric**
Lopinavir 230 mg/m² per dose PO twice daily (maximum 400 mg/dose)

**Adult**
Lopinavir-ritonavir 400-100 mg PO twice daily | 5 days. In select patients with extended ventilation or profound immunosuppression duration may be extended | No adjustments for hepatic or renal dysfunction | Lopinavir/ritonavir suspension available and on formulary in SHGR

May be used in pregnancy

**Major Adverse Events:**
- Oral aversion
- Significant diarrhea
- Acute pancreatitis

**Other Considerations:**
- Significant drug-drug interactions via CYP P450 inhibition
- Some studies used in combination with high dose ribavirin

Neonatal
Lopinavir 300 mg/m² per dose PO twice daily (or 16 mg/kg per dose)

Pediatric
Lopinavir 230 mg/m² per dose PO twice daily (maximum 400 mg/dose)

Adult
Lopinavir-ritonavir 400-100 mg PO twice daily
| Remdesivir: nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase | Inhibits SARS-CoV-2 in vitro\(^5\)  
Has demonstrated *potent in vitro* and *in vivo* activity in animal models against MERS and SARS (as well as all other known coronaviruses)  
Only used in small numbers of patients with SARS-CoV-2 but clinical trials ongoing | Neonatal  
**Pediatric**  
< 40 kg: 5 mg/kg per dose IV once daily on day 1, followed by 2.5 mg/kg per dose IV once daily  
> 40 kg: 200 mg IV once daily on day 1, followed by 100 mg IV once daily  
**Adult**  
200 mg IV once daily on day 1, followed by 100 mg IV once daily  
Available only by compassionate use from Gilead: gilead.com/purpose/advancing-global-health/covid-19  
Link for compassionate use: [https://rdvcu.gilead.com/](https://rdvcu.gilead.com/) | Per protocol – See last column for inclusion and exclusion  
Patients with renal/hepatic dysfunction or dialysis are excluded from compassion use and clinical trials. | Compassionate use Inclusion:  
- Hospitalization with confirmed COVID-19  
- Mechanical ventilation  
Exclusion:  
- Multi-organ failure  
- Requiring vasopressors  
- ALT levels > 5x upper normal limit  
- CrCl < 30 mL/min or any dialysis  
Major Adverse Events:  
- Mild hepatic toxicity  
- GI intolerance |

\(^5\)Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. DOI: [https://doi.org/10.1038/s41422-020-0282-0](https://doi.org/10.1038/s41422-020-0282-0)
| **Tocilizumab**: IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients | Small report of 21 patients with severe hypoxia and intubation showed possible improvement of respiratory function following therapy. Spectrum Health Use Criteria: SHMG Immunology will be reviewing all cases of COVID-19 and recommending therapy. Contact Dr. Nicholas Hartog with any questions. | Pediatric<br>&lt;6 kg: 12 mg/kg<br>6-10 kg: 80 mg<br>10-14 kg: 160 mg<br>15-18 kg: 200 mg<br>19-21 kg: 240 mg<br>22-24 kg: 280 mg<br>25-27 kg: 320 mg<br>28-32 kg: 360 mg<br>33-60 kg: 400 mg<br>&gt;60 kg: adult dosing | Under direction of SHMG Allergy & Immunology | No dose adjustment for renal or hepatic disease | REMS Program for CAR-T, pharmacy must always maintain stock. | Avoid use in pregnancy<br>Major Adverse Events: • Hepatic toxicity<br>Monitoring: • Tb QuantiFERON • LFTs • CBC<br>Contraindications: • Active Tb

| **Anakinra**: IL-1 receptor antagonist | Spectrum Health Use Criteria: SHMG Immunology will be reviewing all cases of COVID-19 and recommending therapy. Contact Dr. Nicholas Hartog with any questions. | Pediatric<br>2 mg/kg per day SQ<br>**Max single dose**: 100mg | Under direction of SHMG Allergy & Immunology | CrCl &lt; 30mL/min: Consider administering prescribed dose every other day | Avoid use in pregnancy<br>Monitoring: • Tb QuantiFERON • CBC<br>Contraindications: • Active Tb

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Adjunctive medications:

- Antiviral:
  - If influenza test positive, start oseltamivir 75 mg BID in all adult patients with normal renal function
    - (Adjust for pediatric patients and those with renal insufficiency)
  - Considerations for empiric treatment for bacterial pneumonia:
    - Based on current literature review there is no unusual associations between COVID-19 infection and bacterial co-infection. Routine initiation of antibiotic therapy for bacterial pneumonia in patient with confirmed COVID-19 infection is not indicated. If based on clinical presentation and labs there is a concern for bacterial superinfection, patients can be managed as per our standard institutional guidelines regarding antibiotic use in patients with suspected pneumonia.
    - Utility of procalcitonin in diagnosis of bacterial pneumonia in COVID-19 patients is questionable - it has been observed and procalcitonin remains slow for 7-10 days and then elevate regardless of presence of bacterial infection.

Medications to Avoid: Consideration should be given to the avoidance of the medications listed below unless benefit outweighs the risk for their use in patients with presumed or proven COVID-19

- **Corticosteroids** - No clinical data exist to indicate that net benefit is derived from corticosteroids in the treatment of respiratory infection due to RSV, influenza, SARS-CoV, or MERS-CoV. The available observational data suggest increased mortality and secondary infection rates in influenza, impaired clearance of SARS-CoV and MERS-CoV, and complications of corticosteroid therapy in survivors. If it is present, the effect of steroids on mortality in those with septic shock is small and is unlikely to be generalizable to shock in the context of severe respiratory failure due to 2019-nCoV.7
  - Overall, no unique reason exists to expect that patients with 2019-nCoV infection will benefit from corticosteroids, and they might be more likely to be harmed with such treatment.7
- **Darunavir based treatment regimens** – There are no clear evidence that Darunavir based treatment regimens (Darunavir/cobicistat & Darunavir/ritonavir) provide any benefit to patients with COVID-19 and are potentially harmful. These medications should not be used to treat patients with COVID-19.
- **NSAIDs** – some experts believe that use of NSAIDS in patients with COVID-19 may aggravate the disease. There is no clear clinical data to support this claim. Currently, there are no clear recommendations to avoid NSAIDs in patients with COVID-19. If possible, consideration should be given to acetaminophen.
- **Nitazoxanide** - There are no clear evidence that nitazoxanide provides any benefit to patients with COVID-19

7Clinical evidence does not support corticosteroid treatment for 2019-nCOV lung injury. https://doi.org/10.1016/S0140-6736(20)30317-2

Questions?

- Nicholas Hartog, MD – SHMG/HDVCH Allergy & Immunology
- Amanda Holsworth, DO – SHMG/HDVCH Allergy & Immunology
- Rosemary Olivero, MD – HDVCH Pediatric Infectious Diseases
- Sara Ogrin, PharmD, BCPPS, BCIDP – Clinical Pharmacy Specialist, Pediatric Infectious Diseases
- Gordana Simeunovic, MD – SHMG Adult Infectious Diseases
- Derek Vander Horst, PharmD, BCPS, BCIDP – Clinical Pharmacy Specialist, Adult Infectious Diseases