
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 suspected/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 Presumed or 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 clinically presumed or confirmed COVID-19

Baseline Orders – See Table 1

Non-ICU Admission

ICU Admission

Immunocompromised OR Pre-existing lung disease

Begin Hydroxychloroquine*

Treatment Pearls - See Table 3

Repeat daily labs – See Table 1

High Risk

Perform Risk Stratification

See Table 2

NOTE: For special populations – See Table 4

Non-High Risk No pharmacologic treatment indicated, continue close monitoring & supportive care

Repeat daily labs – See Table 1

NOTE: All cases of COVID-19 treated with pharmacologic therapy will be reviewed by SH Adult & Pediatric Antimicrobial Stewardship Program for appropriateness.

NOTE: Routine ID consultation is not required for mild-moderate cases

If lack of clinical improvement, consider ID consultation

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

Labs to be reviewed by SHMG Allergy & Immunology daily for ordering of tocilizumab or anakinra

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

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.
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. 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

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

<table>
<thead>
<tr>
<th>History</th>
<th>Clinical Criteria</th>
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<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>
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<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>
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<tr>
<td></td>
<td>Absolute lymphocytes &lt; 0.8</td>
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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 lot 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>Special Populations</th>
<th>Treatment Recommendations</th>
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</table>
| **Cardiovascular Disease**    | - *Statins*<sup>1</sup> - 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*<sup>1</sup> - 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>Hydroxychloroquine: Blocks acidification of endosome, lysosome, Golgi; blocks fusion and possibly uncoating</td>
<td>More potent at inhibiting SARS-Co-V-2 than chloroquine <em>in vitro</em>&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Neonatal&lt;br&gt;Pediatric&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;Adult&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). Unable to find clear studies on 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>
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<sup>1</sup> 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).*
| Chloroquine: Blocks acidification of endosome, lysosome, Golgi; blocks fusion and possibly uncoating | Reduced hospital stay and progression on pneumonia\(^2\) in uncontrolled study | Neonatal Pediatric 8.3 mg/kg per dose PO twice daily (maximum 500 mg per dose) Adult 500mg (300mg base) PO twice daily | 5 days. In select patients with extended ventilation or profound immunosuppression duration may be extended | Adult: GFR < 10mL/min OR HD: 250mg (150mg base) twice daily CRRT: No dose adjustments | 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 |

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\(^3\) 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
| **Remdesivir:** nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase | **Inhibits SARS-CoV-2 in vitro** | **Neonatal** | **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 |

Under the direction of Adult and Pediatric Infectious Diseases  

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  

**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/  

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
| **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. | Pediatric  
<6 kg: 12 mg/kg  
6-10 kg: 80 mg  
10-14 kg: 160 mg  
15-18 kg: 200 mg  
19-21 kg: 240 mg  
22-24 kg: 280 mg  
25-27 kg: 320 mg  
28-32 kg: 360 mg  
33-60 kg: 400 mg  
>60 kg: adult dosing  
**Adult**  
50-60 kg: 400 mg IV  
>60-85 kg: 600 mg IV  
>85 kg: 800 mg IV  
Use actual body wt.  
Doses may be repeated up to every 8 hours for max of 3 doses over 24 hours  
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  
**Major Adverse Events:**  
- Hepatic toxicity  
**Monitoring:**  
- Tb QuantiFERON  
- LFTs  
- CBC  
**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  
2 mg/kg per day SQ  
**Max single dose:** 100mg  
**Adult**  
100mg per day SQ, can consider increase to twice daily if no response  
Under direction of SHMG Allergy & Immunology  
CrCl < 30mL/min: Consider administering prescribed dose every other day  
Avoid use in pregnancy  
**Monitoring:**  
- Tb QuantiFERON  
- CBC  
**Contraindications:**  
- Active Tb |
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. If 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.  
- 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

Clinical 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