

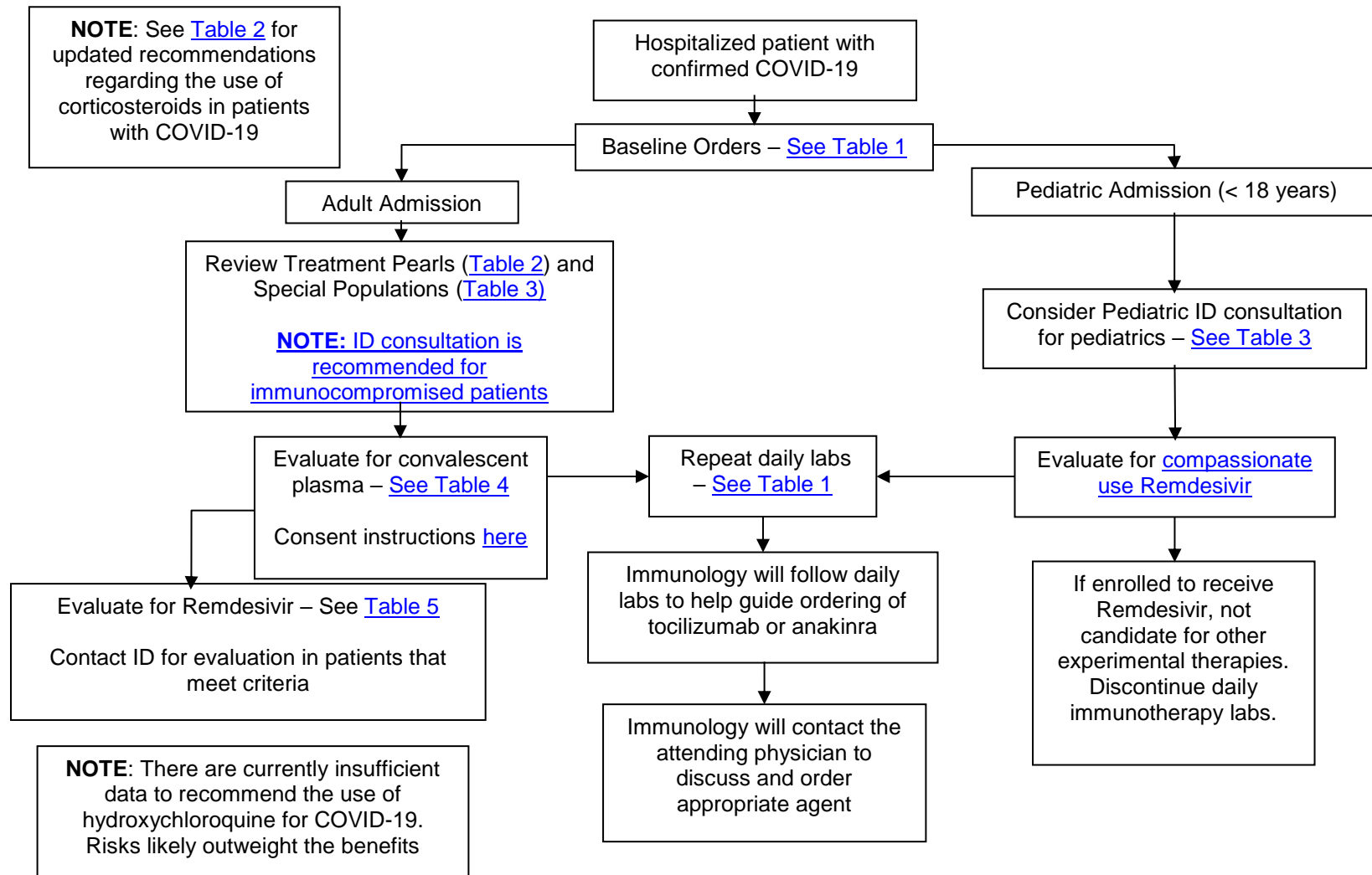
# Therapeutic Options for Treatment of COVID-19 – August 10, 2020 1500

Spectrum Health contact: Derek Vander Horst \*Highlight 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**



**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 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 &

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 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).
6. Concomitant bacterial pneumonia appears to be rare in patients with confirmed COVID-19. Re-evaluate need for antibiotic therapy daily.
7. There is insufficient evidence to support the routine addition of azithromycin to hydroxychloroquine for the experimental treatment of COVID-19.
8. Routine ID consultation is not required for mild-moderate cases. If lack of clinical improvement, consider ID consultation.

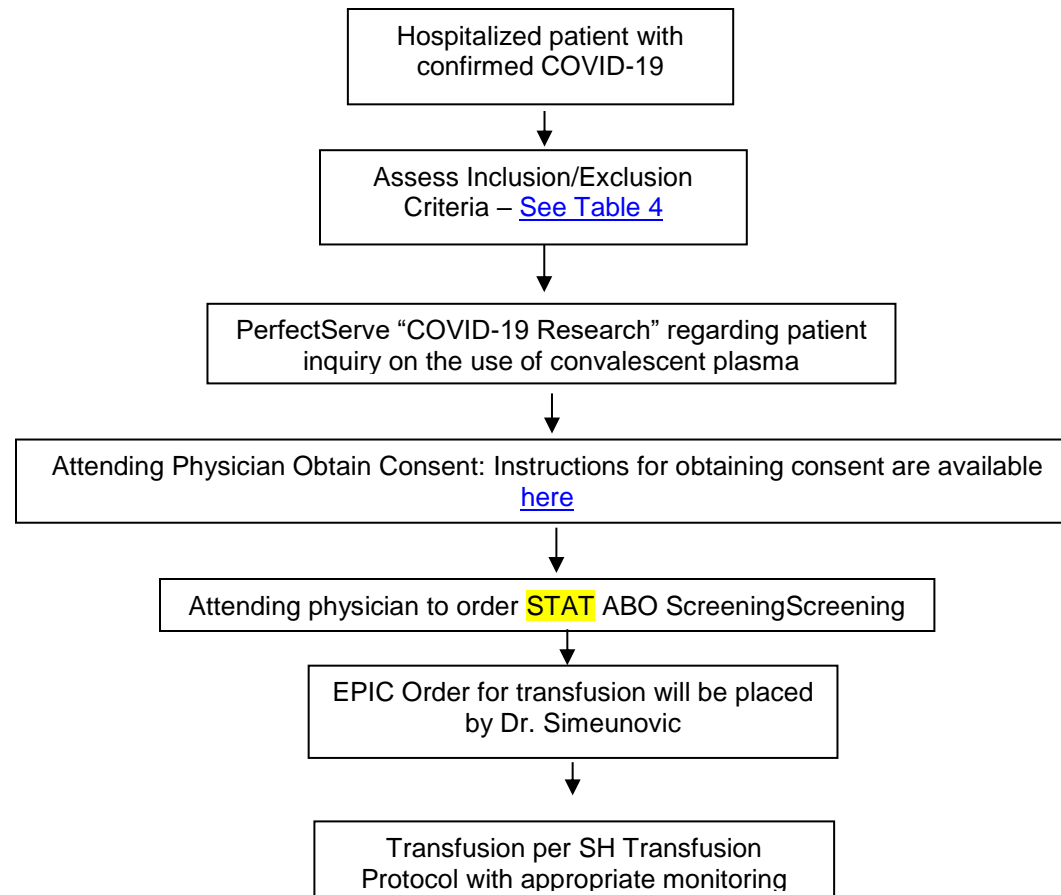
**Corticosteroids:**

1. Dexamethasone may be considered in all hospitalized COVID-19 patients with ≥ 7 days of symptoms AND a new or worsening requirement for supplemental oxygen.
  - a. Patients with less than 7 days of symptoms AND a new or worsening requirement for supplemental oxygen with risk factors for decompensation may be considered on a case-by-case basis.

- b. Patients that are stable, without new or worsening oxygen requirements, should not be treated with corticosteroids unless otherwise indicated.
- c. Dexamethasone is the preferred corticosteroid in the treatment of COVID-19. Alternative corticosteroids for COVID-19 patients may be used at the discretion of the treating provider on a case by case basis.
- 2. Dexamethasone COVID-19 Dosing – NOTE: the oral formulation is preferred for patients able to tolerate:
  - a. *Adult Dosing:* 6mg PO or IV once daily
  - b. *Pediatric Dosing:* 0.15 mg/kg (Max Dose 6mg) PO or IV once daily
  - c. *Duration:* 10 days or discharge (whichever sooner)
- 3. Dexamethasone should not be prescribed at discharge and there is no need to taper the above steroid regimen.

Cardiovascular Disease	<ul style="list-style-type: none"> <li>• <i>Statins</i> - 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.               <ul style="list-style-type: none"> <li>○ Patients without a cardiovascular indication for statin therapy should <u>not</u> be started on a statin for the treatment of COVID-19.</li> </ul> </li> <li>• <i>ACE Inhibitors/ARBs</i> - 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.</li> </ul>
Pregnancy	<ul style="list-style-type: none"> <li>• 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.</li> <li>• For hospitalized patients, consider pulmonary OR infectious disease consult</li> <li>• Decisions about the use of corticosteroids for fetal lung maturity should be made in consultation with ID specialists and maternal-fetal medicine consultants</li> </ul>
Children < 18 years	<ul style="list-style-type: none"> <li>• PEDS ID consults are only recommended if worsening respiratory status or severely ill for patients admitted with COVID-19. Any consideration of treatment should be discussed with PEDS ID.</li> </ul>
Immunocompromised Patients	<ul style="list-style-type: none"> <li>• Infectious Diseases consultation is recommended for all solid organ and bone marrow transplant patients</li> </ul>
Post-Exposure Prophylaxis	<ul style="list-style-type: none"> <li>• CDC does <b>NOT</b> endorse post-exposure prophylaxis for people who may have been exposed to COVID-19 at this time</li> </ul>

Figure 2- Individual Use of Convalescent Plasma for The Treatment of PCR Confirmed COVID-19



<b>Table 4 – Treatment of COVID-19 with Convalescent Plasma</b>	
Contact Dr. Gordana Simeunovic (SHMG Adult Infectious Diseases) for all questions regarding the use of convalescent plasma in the treatment of COVID-19.	
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Hospitalized for PCR confirmed COVID-19,</li> <li>2. Patient at least 18 years of age,</li> <li>3. Patient or POA willing and able to provide written informed consent,</li> <li>4. Meets criteria for:               <ul style="list-style-type: none"> <li>○ <u>Severe illness with potential for progression to life threatening disease defined as:</u> <ul style="list-style-type: none"> <li>▪ Dyspnea</li> <li>▪ Respiratory rate <math>\geq</math> 30 breaths per minute</li> <li>▪ O<sub>2</sub> saturation <math>\leq</math> 93%</li> <li>▪ PaO<sub>2</sub>/FiO<sub>2</sub> ratio &lt; 300</li> <li>▪ Lung infiltrates progression &gt; 50% in 24-48 hours</li> </ul> </li> <li><b>OR</b></li> <li>○ <u>Life threatening disease defined as:</u> <ul style="list-style-type: none"> <li>▪ Respiratory failure</li> <li>▪ Septic shock</li> <li>▪ Multisystem organ failure</li> </ul> </li> </ul> </li> </ol>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Greater than 14 days since onset of COVID-19 symptoms</li> <li>• Patients in terminal stage of disease</li> <li>• Female with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period</li> <li>• Receipt of pooled immunoglobulin in past 30 days</li> <li>• Known IgA deficiency</li> <li>• Contraindications to transfusion, possibly including a history of prior life-threatening allergic reactions to transfusion of blood products</li> <li>• Clinical evidence (in the judgment of site investigator) that etiology of illness is not primarily COVID-19 related</li> <li>• Medical condition in which receipt of therapeutic volume of plasma (possibly even 500ml), administered following blood product administration guidelines, is considered to cause more harm than benefits to patient</li> </ul>

<b>Table 5 – Treatment of COVID-19 with Remdesivir via FDA Emergency Use Authorization</b>	
Contact Derek Vander Horst (SHGR Pharmacy) or Infectious Diseases on call for all questions regarding the use of Remdesivir in the treatment of COVID-19 on a case-by-case basis.	
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Hospitalized for PCR confirmed COVID-19,</li> <li>2. At least 18 years of age,</li> <li>3. At least 40kg actual body weight,</li> <li>4. Duration of symptoms <math>\leq</math> 7 days,</li> <li>5. eGFR &gt;30 mL/min,</li> </ol>

	<p>6. LFTs &lt; 5X upper limit of normal,</p> <p>7. Clinical criteria:</p> <ul style="list-style-type: none"> <li>○ Acute respiratory failure requiring ventilatory support /ECMO for less than 24 hours</li> </ul> <p>Severe disease defined as SpO2 &lt; 93% on room air requiring supplemental oxygen <b>and</b> pulmonary infiltrates on imaging <b>with</b> risk for progression to intubation (immunosuppression, chronic lung disease, cardiovascular disease, morbid obesity, uncontrolled DM with HgA1C &gt;8)</p>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Hypersensitivity to any component of Remdesivir</li> <li>• Terminal stage of the disease</li> <li>• Current presentation not primarily related to COVID-19 as per treating physician judgement</li> </ul>

Therapeutic Agent & Mechanism	Data on Use	Dosing Strategies	Duration of Therapy	Renal Dosing	Monitoring/Considerations
<p><b>Remdesivir:</b> nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase</p> <p>Under the direction of Adult and Pediatric Infectious Diseases</p>	<p>Inhibits SARS-CoV-2 in vitro<sup>1</sup></p> <p>Has demonstrated <i>potent in vitro</i> and <i>in vivo</i> activity in animal models against MERS and SARS (as well as all other known coronaviruses)</p> <p>Only used in small numbers of patients with SARS-CoV-2 but clinical trials ongoing</p>	<p>Neonatal</p> <p><u>Pediatric</u> &lt; 40 kg: 5 mg/kg per dose IV once daily on day 1, followed by 2.5 mg/kg per dose IV once daily &gt; 40 kg: 200 mg IV once daily on day 1, followed by 100 mg IV once daily</p> <p><u>Adult</u> 200 mg IV once daily on day 1, followed by 100 mg IV once daily</p> <p>Available by FDA EUA or via compassionate use from Gilead.</p>	5 or 10 days	Patients with renal/hepatic dysfunction or dialysis are excluded from compassionate use and clinical trials.	<p>Compassionate use available only or pediatrics (Age &lt; 18) or pregnant women.</p> <p>Inclusion:</p> <ul style="list-style-type: none"> <li>• Hospitalization with confirmed COVID-19</li> <li>• Mechanical ventilation</li> </ul> <p>Exclusion:</p> <ul style="list-style-type: none"> <li>• Multi-organ failure</li> <li>• Requiring vasopressors</li> <li>• ALT levels &gt; 5x upper normal limit</li> <li>• CrCl &lt; 30 mL/min or any dialysis</li> </ul> <p>Major Adverse Events:</p>

<sup>1</sup> Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. DOI: <https://doi.org/10.1038/s41422-020-0282-0>

		Link for compassionate use: <a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a>			<ul style="list-style-type: none"> <li>• Mild hepatic toxicity</li> <li>• GI intolerance</li> </ul>
--	--	--	--	--	---

<b>Table 6 – Criteria for Use of Immunomodulating Therapy (Only to be ordered under direction from SHMG Allergy &amp; Immunology)</b>	
Contact Dr. Nick Hartog for all questions regarding the use of immunomodulators in the treatment of COVID-19.	
Inclusion Criteria	<ul style="list-style-type: none"> <li>• Hospitalized for PCR confirmed COVID-19,</li> <li>• Worsening respiratory status in last 24 hours <b>and</b> on ≥4L NC or intubated (for adults)</li> <li>• &lt;14 days into current illness (if duration is noted)</li> <li>• Assessment by SHMG Allergy &amp; Immunology</li> </ul>
Exclusion Criteria	<ul style="list-style-type: none"> <li>• Metastatic CA</li> <li>• DNI or where escalation of care would not be pursued based on goals of care</li> <li>• LVEF &lt; 30%</li> <li>• CKD on dialysis at baseline</li> <li>• Cardiac arrest in hospital</li> </ul>

<p><b>Tocilizumab:</b> IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients</p> <p>Under the direction of Adult Infectious Diseases or Allergy &amp; Immunology</p>	<p>Small report of 21 patients with severe hypoxia and intubation showed possible improvement of respiratory function following therapy</p> <p><u>Spectrum Health Use Criteria:</u> SHMG Immunology will be reviewing all</p>	<p><u>Pediatric</u></p> <p>&lt;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 &gt;60 kg: adult dosing</p> <p><u>Adult</u></p>	Under direction of SHMG Allergy & Immunology	No dose adjustment for renal or hepatic disease	<p>REMS Program for CAR-T, pharmacy <b>must</b> always maintain stock.</p> <p>Major Adverse Events:</p> <ul style="list-style-type: none"> <li>• Hepatic toxicity</li> </ul> <p>Monitoring – Labs to be discussed with Immunology and obtained (but do not</p>
--	---	---	--	---	--



	cases of COVID-19 and recommending therapy. Contact Dr. Nicholas Hartog with any questions.	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			need to have resulted) prior to administration. <ul style="list-style-type: none"> <li>Tb QuantiFERON</li> <li>LFTs</li> <li>CBC</li> </ul> Contraindications: <ul style="list-style-type: none"> <li>Active Tb</li> </ul>
<b>Anakinra:</b> IL-1 receptor antagonist  Under the direction of Adult Infectious Diseases or Allergy & Immunology	<u>Spectrum Health Use Criteria:</u> SHMG Immunology will be reviewing all cases of COVID-19 and recommending therapy. Contact Dr. Nicholas Hartog with any questions.	<u>Pediatric</u> 2 mg/kg per day SQ <b>Max single dose:</b> 100mg  <u>Adult</u> 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	Monitoring – Labs to be discussed with Immunology and obtained (but do not need to have resulted) prior to administration: <ul style="list-style-type: none"> <li>Tb QuantiFERON</li> <li>CBC</li> </ul> Contraindications: <ul style="list-style-type: none"> <li>Active Tb</li> </ul>

<sup>6</sup>COVID-19: consider cytokine storm syndromes and immunosuppression. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0); Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)

### 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

- Chloroquine - Due to lack of *in vivo* safety & efficacy data, Spectrum Health does not recommend the use of chloroquine for COVID-19.
- *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.
- *Hydroxychloroquine* – Due to lack of *in vivo safety* & efficacy data, Spectrum Health does not recommend the use of hydroxychloroquine for COVID-19.
- *Lopinavir/ritonavir* - Due to lack of *in vivo safety* & efficacy data, Spectrum Health does not recommend the use of lopinavir/ritonavir for 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.
- *Ivermectin* – *In vitro* data suggests antiviral activity. To achieve the appropriate levels for antiviral activity *in vivo*, the dose would need to be increased far beyond maximum doses for human use. Ivermectin should not be used for the treatment of COVID-19.
- *Nitazoxanide* - There are no clear evidence that nitazoxanide provides any benefit to patients with COVID-19
- *Vitamin & Mineral Supplements (Vitamin C/D, Zinc, etc.)* – There are no data to suggest benefit on clinical outcomes with the use of these supplements either as monotherapy or in combination with any experimental therapies. They should NOT be used if patient is to be enrolled, or is enrolled, in a clinical trial.

### 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