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

Spectrum Health contact: Gretchen Koeman

*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

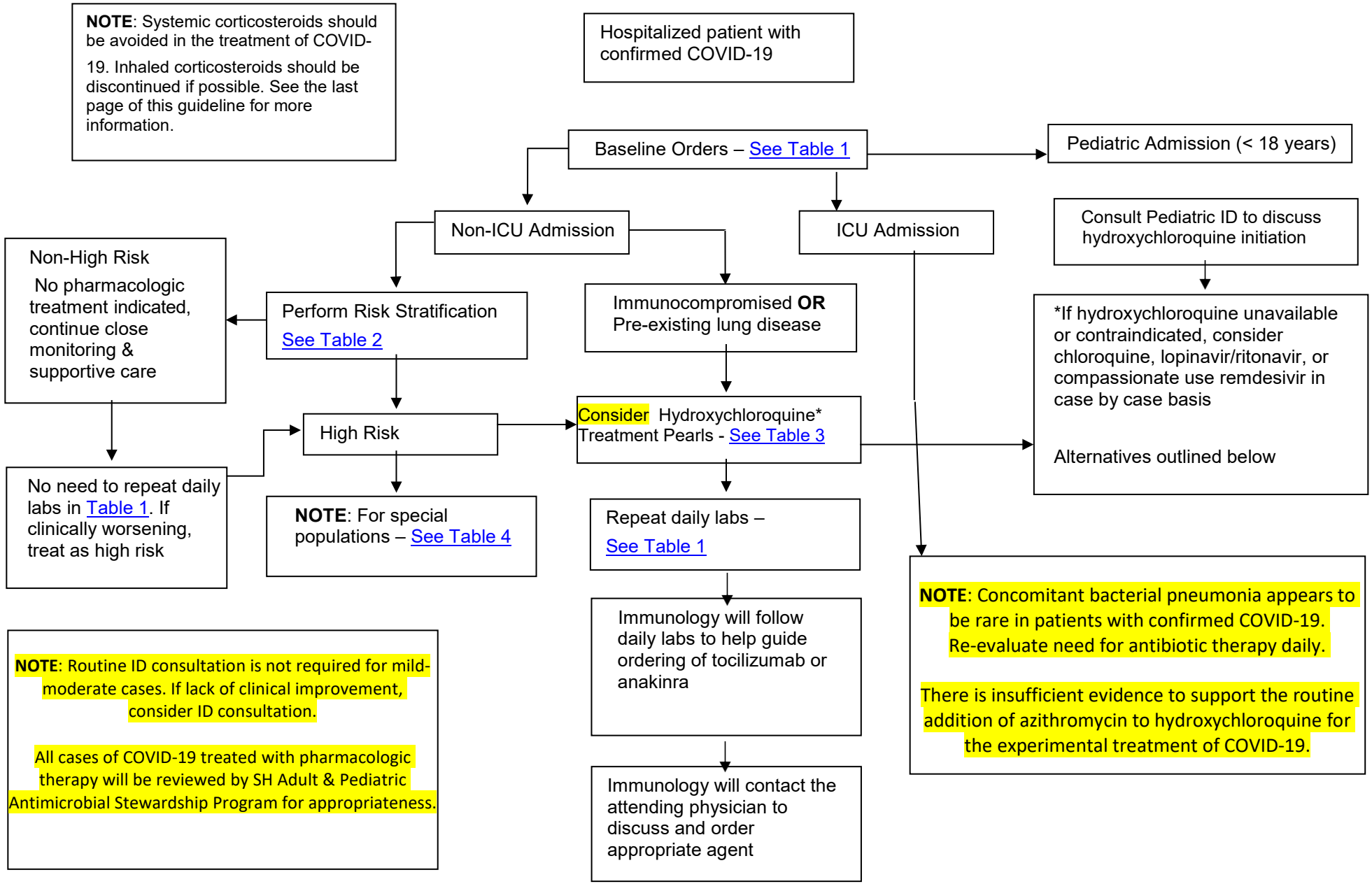

Table 1 – Spectrum Health Recommended COVID-19 Laboratory Monitoring

The labs labeled below will be evaluated by SHMG Allergy & Immunology peripherally to assess for inhiation 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 & 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

History	Clinical Criteria
• Age ≥ 60 years • History of cardiovascular disease • ESRD • Diabetes (A1C ≥7.6)	• O_2 saturation < 90% on room air or baseline O_2 • D-dimer > 1000 ng/mL • LDH > 245 U/L • CRP > 20 mg/L • Absolute lymphocytes < 0.8

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	
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 <u>not</u> 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
Children < 18 years	• Pediatric Infectious Diseases Consultation Recommended
Immunocompromised Patients	• Begin treatment with hydroxychloroquine or alternative therapy as indicated. Infectious Diseases consultation is recommended for all solid organ and bone marrow transplant patients
Post-Exposure Prophylaxis	• CDC does **NOT** endorse post-exposure prophylaxis for people who may have been exposed to COVID-19 at this time

Therapeutic Agent & Mechanism	Data on Use	Dosing Strategies	Duration of Therapy	Renal Dosing	Monitoring/Considerations
Hydroxychloroquine: Blocks acidification of endosome, lysosome, Golgi; blocks fusion and possibly uncoating	More potent at inhibiting SARS-Co- V-2 than chloroquine *in vitro*[1]	Neonatal Pediatric 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) Adult 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	5 days. In select patients with extended ventilation or profound immunosuppression duration may be extended	No renal or hepatic adjustments necessary	May be used in pregnancy Extemporaneously prepared suspension (25 mg/mL) available for enteral tube administration. Major Adverse Events: • GI intolerance • QTc prolongation • Hypoglycemia Consider monitoring for QTc prolongation; especially when using with other QTC prolonging medications No need for G6PD deficiency screening prior to therapy

[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).

Chloroquine: Blocks acidification of endosome, lysosome, Golgi; blocks fusion and possibly uncoating	Reduced hospital stay and progression on pneumonia[2] in uncontrolled study Inhibits SARS-CoV-2 in vitro[3] Less potent at inhibiting SARS-Co-V-2 than hydroxychloroquine *in vitro*[4]	Neonatal <u>Pediatric</u> 8.3 mg/kg per dose PO twice daily (maximum 500 mg per dose) <u>Adult</u> 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

[2] Colson P et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. DOI: https://doi.org/10.1016/j.ijantimicag.2020.105932

[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 <u>lopinavir</u> component <u>Neonatal</u> Lopinavir 300 mg/m^2 per dose PO twice daily (or 16 mg/kg per dose) <u>Pediatric</u> Lopinavir 230 mg/m^2 per dose PO twice daily (maximum 400 mg/dose) <u>Adult</u> 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 Under the direction of Adult and Pediatric Infectious Diseases	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 <u>Pediatric</u> < 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 <u>Adult</u> 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/	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

Tocilizumab: IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients Under the direction of Adult Infectious Diseases or Allergy & Immunology	Small report of 21 patients with severe hypoxia and intubation showed possible improvement of respiratory function following therapy <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> <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 <u>Adult</u> 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 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 **Max single dose:** 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	Avoid use in pregnancy Monitoring: • Tb QuantiFERON • CBC Contraindications: • Active Tb

[6]COVID-19: consider cytokine storm syndromes and immunosuppression. 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

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

[7] 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