

Spectrum Health Guidelines for the Management of COVID-19 due to SARS-CoV-2 – 10.29.2020, 1600

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Document reviewed: 10.29.20

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 enrolled in a clinical trial for monoclonal antibody therapy (aSPIKE) 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.
- Remdesivir is the only FDA approved treatment of hospitalized patients with COVID-19. The other therapeutic 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.
- 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 Adult Patients with Confirmed COVID-19

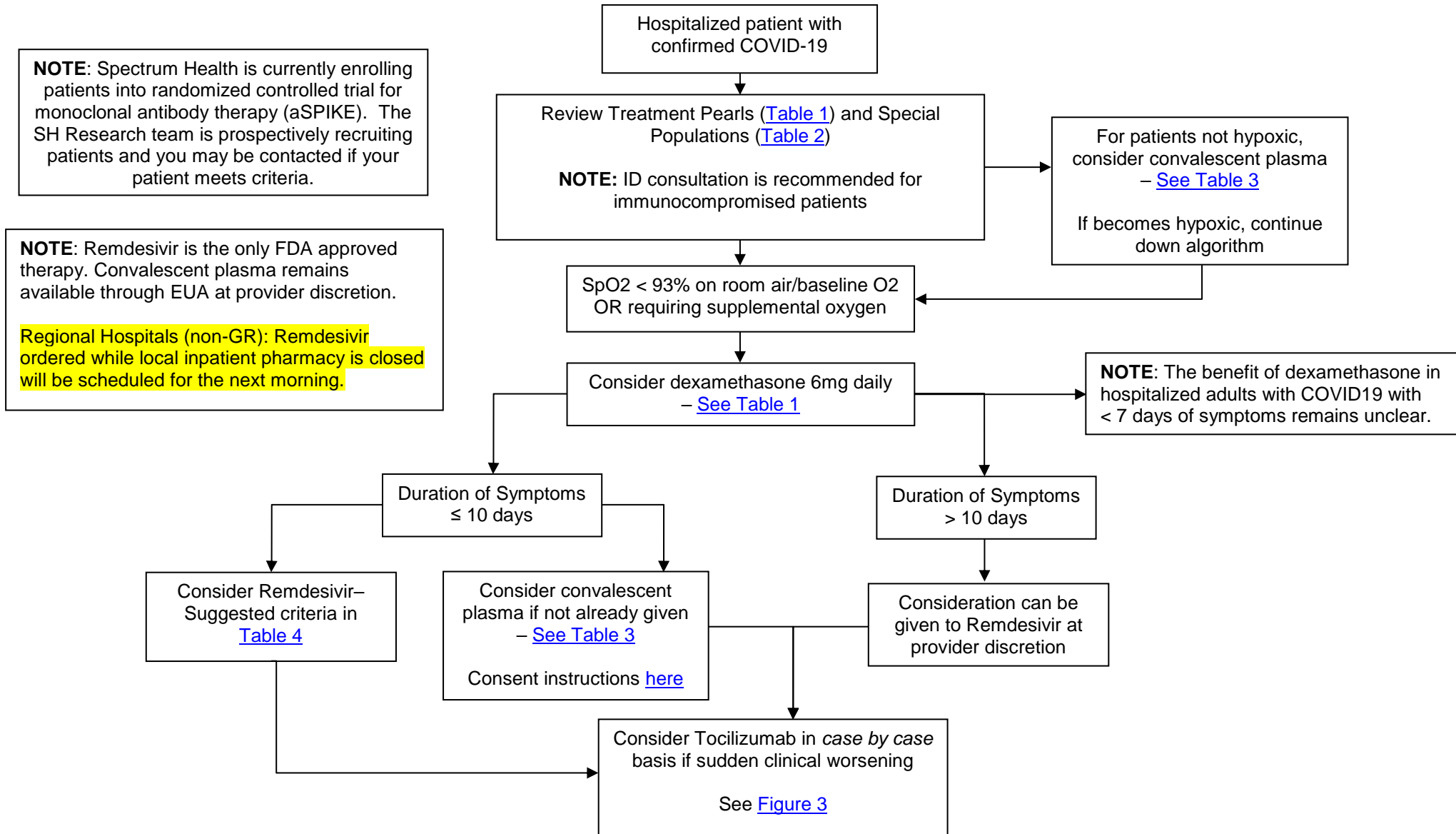


Table 1 - Spectrum Health COVID-19 Treatment Pearls

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 and discontinue therapy if no longer indicated.
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:

- a. Dexamethasone should be considered in all hospitalized COVID-19 patients with ≥ 7 days of symptoms **AND** a new or worsening requirement for supplemental oxygen. Patients that are stable, without new or worsening oxygen requirements, should not be treated with corticosteroids unless otherwise indicated.
 - i. The benefit of dexamethasone in hospitalized adults with COVID19 with < 7 days of symptoms remains unclear.
 - b. 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.

Table 2 – Treatment of COVID-19 in Special Populations	
Cardiovascular Disease	<ul style="list-style-type: none"> • <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"> ○ Patients without a cardiovascular indication for statin therapy should <u>not</u> be started on a statin for the treatment of COVID-19. • <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.
Pregnancy	<ul style="list-style-type: none"> • 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 • 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	<ul style="list-style-type: none"> • Pediatric Infectious Diseases consults are recommended for pediatric patients who have respiratory compromise or are severely ill for with COVID-19, including concern for MIS-C. Any consideration of treatment should be discussed with Pediatric Infectious Diseases.
Immunocompromised Patients	<ul style="list-style-type: none"> • Infectious Diseases consultation is recommended for all solid organ and bone marrow transplant patients
Post-Exposure Prophylaxis	<ul style="list-style-type: none"> • CDC does NOT endorse post-exposure prophylaxis for people who may have been exposed to COVID-19 at this time

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

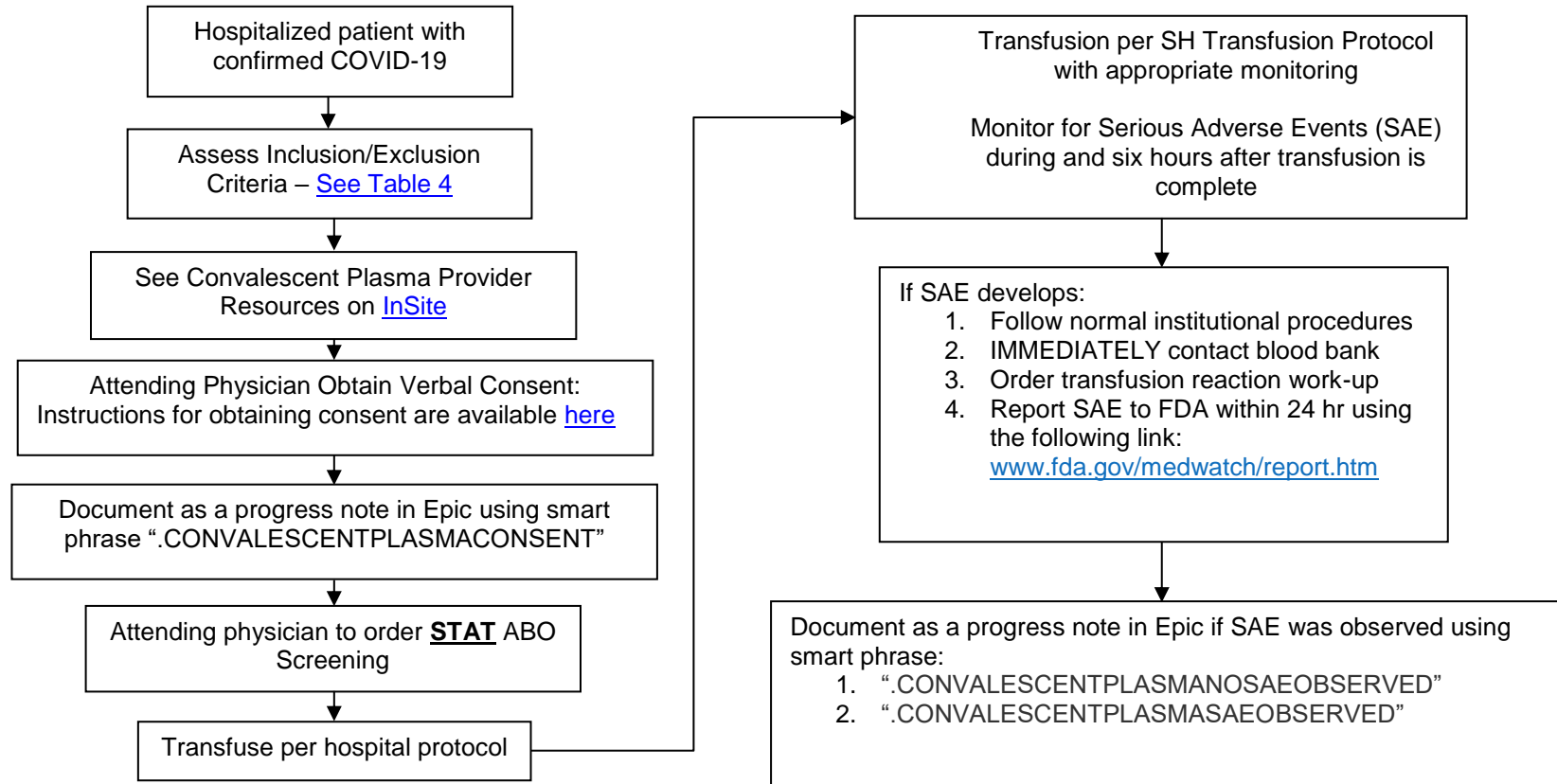


Table 3 – Treatment of COVID-19 with Convalescent Plasma	
Contact Dr. Gordana Simeunovic (SHMG Adult Infectious Diseases) for all questions regarding the use of convalescent plasma in the treatment of COVID-19.	
Inclusion Criteria	<ol style="list-style-type: none"> 1. Hospitalized for PCR confirmed COVID-19, 2. Patient at least 18 years of age, 3. Patient or POA willing and able to provide verbal consent (or may use two-physician concurrence if POA unavailable), 4. Meets criteria for: <ul style="list-style-type: none"> ○ Severe illness with potential for progression to life threatening disease defined as (any of the following): <ul style="list-style-type: none"> ▪ Dyspnea ▪ Respiratory rate \geq 30 breaths per minute ▪ O2 saturation \leq 93% on room air ▪ PaO₂/FiO₂ ratio < 300 ▪ Lung infiltrates progression > 50% in 24-48 hours ○ OR life-threatening disease defined as: <ul style="list-style-type: none"> ▪ Respiratory failure ▪ Septic shock ▪ Multisystem organ failure
Exclusion Criteria	<ol style="list-style-type: none"> 1. > 10 days since the onset of symptoms 2. Patients in terminal stage of disease 3. Female with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period 4. Receipt of pooled immunoglobulin in past 30 days 5. Known IgA deficiency 6. Contraindications to transfusion, possibly including a history of prior life-threatening allergic reactions to transfusion of blood products 7. Clinical evidence (in the judgment of site investigator) that etiology of illness is not primarily COVID-19 related 8. 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

Table 4 – Suggested Criteria for Treatment of Hospitalized Patients COVID-19 with Remdesivir

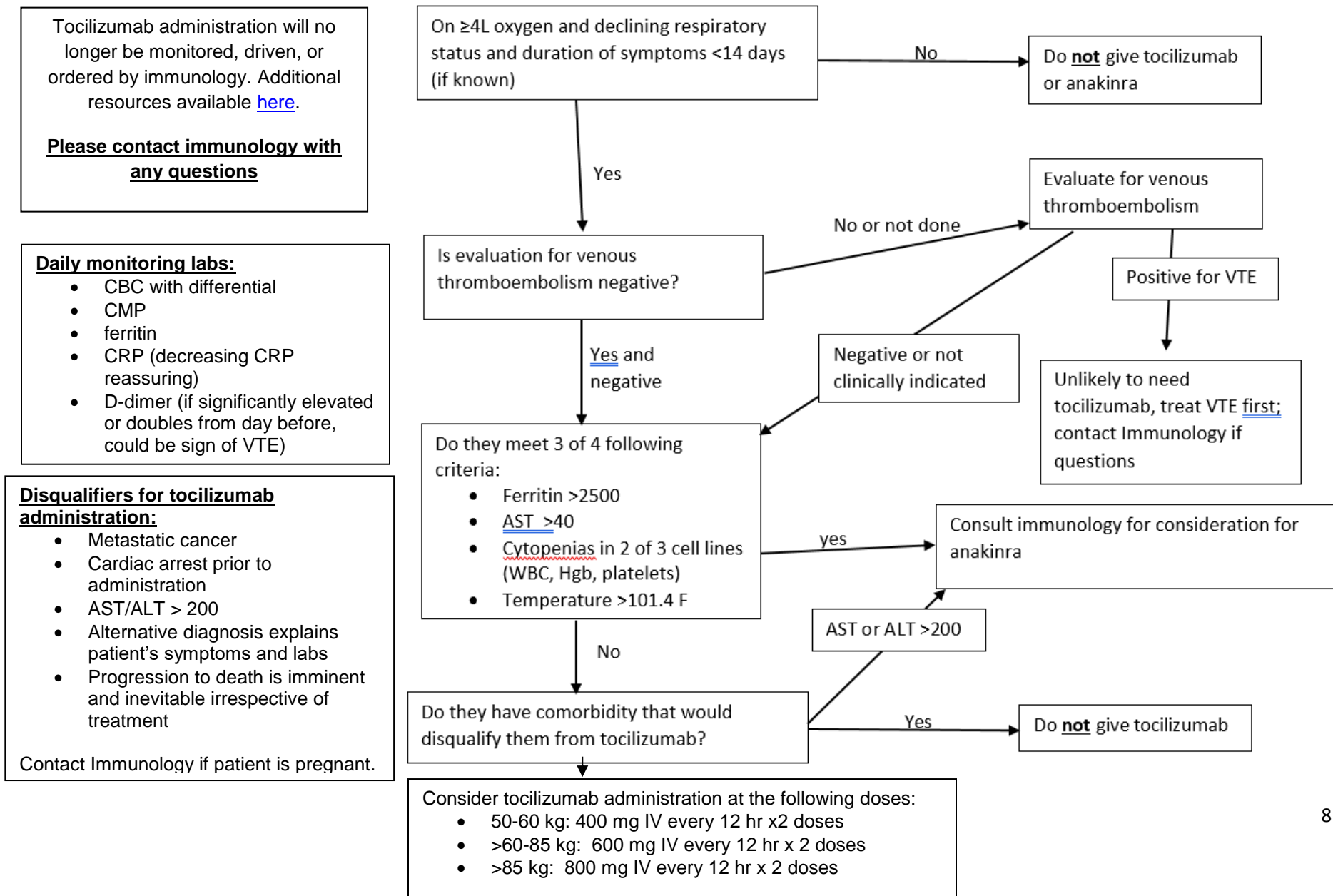
Contact Derek Vander Horst (SHGR Pharmacy) or Infectious Diseases on call if any questions regarding the use of Remdesivir for patients felt to benefit from Remdesivir that do not meet the below criteria. See additional detail [below](#).

Contact Rosemary Olivero (Peds ID HDVCH) or Pediatric Infectious Diseases on call for any children <18 years of age with symptomatic COVID-19 to discuss use of remdesivir.

Inclusion Criteria	Adult Patients (≥18 years of age)	Pediatric Patients (<18 years of age)
	<ol style="list-style-type: none"> 1. Hospitalized for PCR confirmed COVID-19, 2. At least 18 years of age, 3. At least 40kg actual body weight, 4. Duration of symptoms ≤ 10 days, 5. Non-hemodialysis dependent & eGFR ≥ 30 mL/min, 6. LFTs < 10X upper limit of normal, 7. Clinical criteria: <ul style="list-style-type: none"> ○ Acute respiratory failure requiring ventilatory support /ECMO for less than 24 hours ○ Severe disease defined as SpO2 < 93% on room air requiring supplemental oxygen and pulmonary infiltrates on imaging with risk for progression to intubation (immunosuppression, chronic lung disease, cardiovascular disease, morbid obesity, uncontrolled DM with HgA1C >8) 	<ol style="list-style-type: none"> 1. Hospitalized for PCR confirmed COVID-19, 2. Less than 18 years of age, 3. New or increasing oxygen requirement or respiratory compromise, 4. Diagnosis of MIS-C
Exclusion Criteria	<ul style="list-style-type: none"> • Hypersensitivity to any component of remdesivir • Any form of hemodialysis • Current presentation not primarily related to COVID-19 as per treating physician judgement 	<ul style="list-style-type: none"> • Concurrent treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 less than 24 hours prior to study drug dosing • ALT or AST > 5 ULN • eGFR < 30 mL/min/1.73m² using Schwartz formula for participants ≥ 1 year of age OR elevation in creatinine • If < 28 days of age, any major congenital renal anomaly • If < 24 hours of age, Apgar score < 5 when last recorded • Known hypersensitivity to the study drug, the metabolites, or formulation excipient • Positive pregnancy test at screening only for female of childbearing potential

Figure 3 – Suggested Evaluation for Tocilizumab in the Treatment of Hospitalized Adults with COVID-19

While it is likely some subgroups would benefit from IL-6 inhibition, it is not yet clear how to identify this group. Thus far, prospective randomized controlled trials have not shown clear benefit with administration of tocilizumab and COVID-19.^{6,7,8,9} Could be considered in case-by case basis. If considered, below is suggested algorithm:



Therapeutic Agent & Mechanism	Data on Use	Dosing Strategies	Duration of Therapy	Renal Dosing	Monitoring/Considerations
<p>Remdesivir: nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase</p>	<p>Inhibits SARS-CoV-2 in vitro¹</p> <p>Remdesivir has not shown definitive mortality benefit for the treatment of COVID19²</p> <p>Remdesivir may shorten duration of symptoms and length of stay in hospitalized patients with COVID19²</p> <p>The benefit in patients with symptoms greater than 10 days is unclear</p>	<p><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</p> <p><u>Adult</u> 200 mg IV once daily on day 1, followed by 100 mg IV once daily</p>	<p>5 days</p>	<p>Caution for patients with eGFR < 30 mL/min as cyclodextrin may accumulate leading to increased risk of nephrotoxicity – Risk vs benefit for use in this population</p> <p>The dosing of Remdesivir in any dialysis modality is unknown</p>	<p>Major Adverse Events:</p> <ul style="list-style-type: none"> • Hepatic toxicity • Infusion related reactions (hypotension, fever) • Mild-moderate rash <p>Monitoring:</p> <ul style="list-style-type: none"> • CMP & CBC daily

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

² Beigel JH et al. Remdesivir for the Treatment of COVID-19 – Final Report. [N Engl J Med. 2020 Oct 8;NEJMoa2007764](https://doi.org/10.1056/NEJMoa2007764).

<p>Tocilizumab: IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients</p>	<p>While it is likely some subgroups would benefit from IL-6 inhibition, it is not yet clear how to identify this group. Thus far, prospective randomized controlled trials have not shown clear benefit with administration of tocilizumab and COVID-19.^{6,7,8,9}</p> <p>Could be considered in case-by-case basis</p> <p>Contact SHMG Allergy & Immunology with questions</p>	<p><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</p> <p><u>Adult</u> 50-60 kg: 400 mg IV >60-85 kg: 600 mg IV >85 kg: 800 mg IV</p> <p>Use actual body weight</p>	<p>Every 12 hr x 2 doses</p>	<p>No dose adjustment for renal or hepatic disease</p>	<p>REMS Program for CAR-T, pharmacy must always maintain stock.</p> <p>Major Adverse Events:</p> <ul style="list-style-type: none"> • Hepatic toxicity <p>Monitoring:</p> <ul style="list-style-type: none"> • Tb QuantiFERON • LFTs • CBC <p>Contraindications:</p> <ul style="list-style-type: none"> • Active Tb
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⁶ 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)

⁷ Stone JH et al. Efficacy of Tocilizumab in Patients Hospitalized with COVID-19. N Engl J Med. 2020 Oct 21. doi: 10.1056/NEJMoa2028836

⁸ Salvarani C et al. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized with COVID-19 Pneumonia: A randomized Clinical Trial. JAMA Intern Med. 2020 Oct. doi: 10.1001/jamainternmed.2020.6615.

⁹ Hermine O et al. Effect of Tocilizumab vs Usual Care in Adults Hospitalized with COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2020 Oct 20. doi: 10.1001/jamainternmed.2020.6820.

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