# Spectrum Health Guidelines for the Management of COVID-19 due to SARS-CoV-2 – 4.13.2021, 1600

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**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.

SPECTRUM HEALTH

**Figure 1 – Suggestive Management of Hospitalized Adult Patients with Confirmed COVID-19**

**NOTE**: See the COVID-19 Clinical Pathway for recommendations on baseline labs.

With clinical decline, please strongly consider repeating ferritin. If ferritin >2500, contact on call immunology to discuss clinical concern for HLH

**NOTE**: Remdesivir is the only FDA approved therapy.

Regional Hospitals (non-GR): Remdesivir ordered while local inpatient pharmacy is closed will be scheduled for the next morning.

**NOTE**: Recent prospective randomized controlled trials have not shown clear benefit for hospitalized patients with severe COVID-19. Convalescent plasma remains available via FDA EUA and may be considered in case-by case basis in mild to moderate illness. If considered, recommended criteria are listed below (details on Spectrum Health internal site).

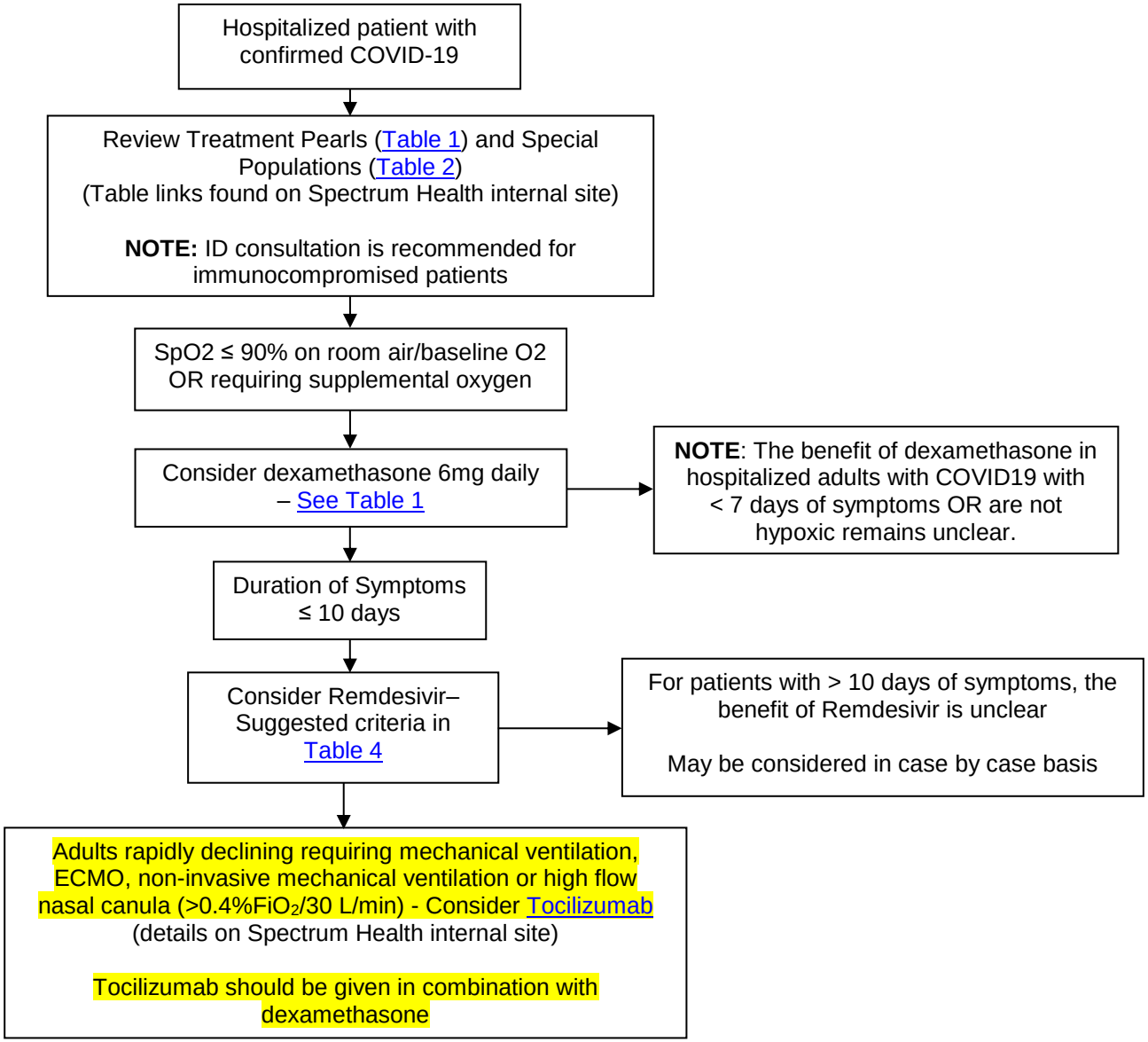


**Table 1 - Spectrum Health COVID-19 Treatment Pearls**

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 – May consider continuing at discharge for patients believed to benefit prior to completion of 10 days

| **Table 2 – 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.<br>  ○ Patients without a cardiovascular indication for statin therapy should <u>not</u> be started on a statin for the treatment of COVID-19.<br>• *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. |
| 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.<br>• For hospitalized patients, consider pulmonary OR infectious disease consult<br>• 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 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 | • 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 |

While some subgroups may benefit from the administration of convalescent plasma, recent prospective randomized controlled trials have not shown clear benefit with its administration for hospitalized patients with severe COVID-19.[1,2] Could be considered in case-by case basis in mild to moderate illness. If considered, recommended criteria are listed below:

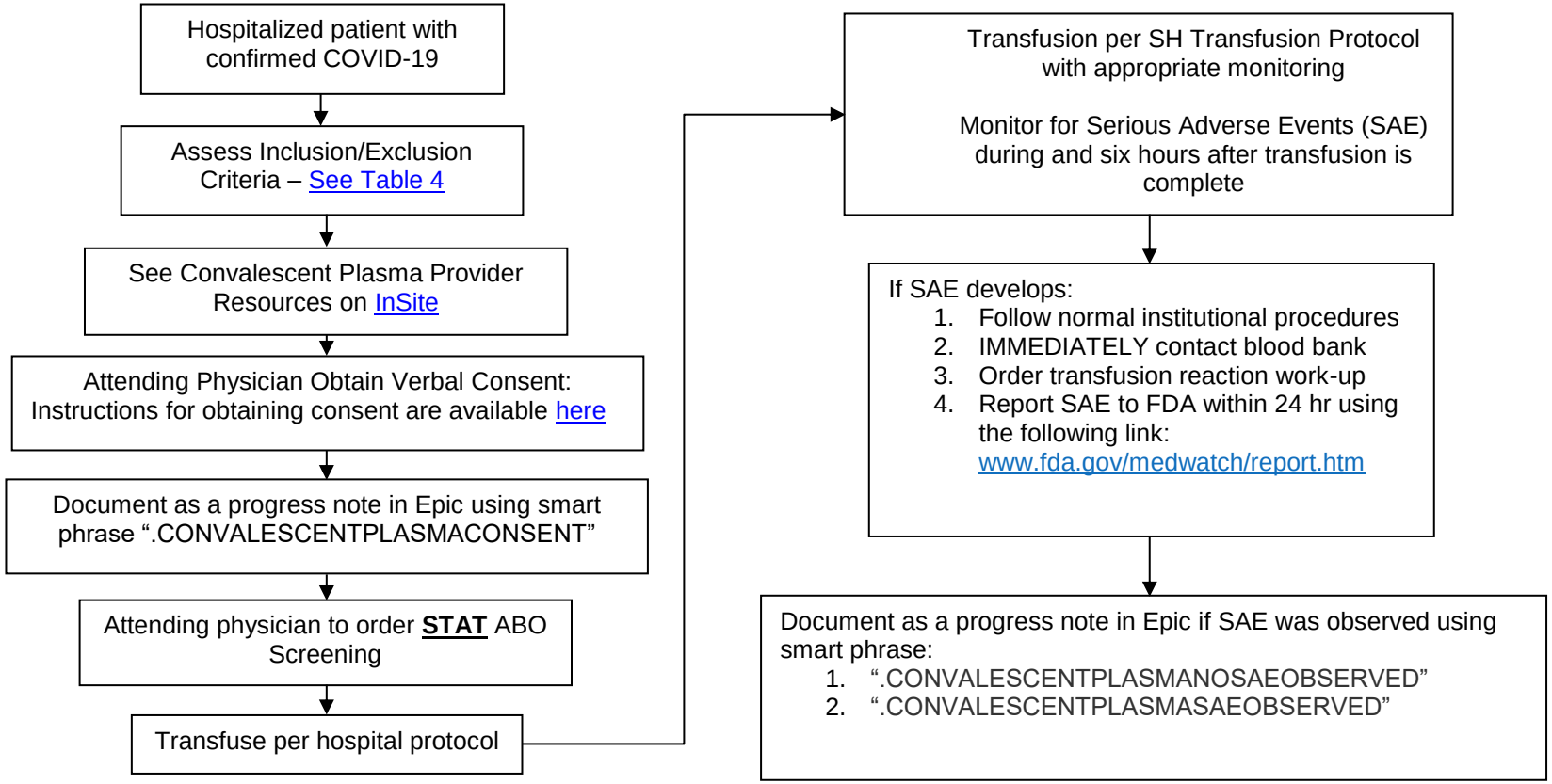
| **Table 3 – Treatment of COVID-19 with Convalescent Plasma**<br>Contact Dr. Gordana Simeunovic (SHMG Adult Infectious Diseases) for all questions regarding the use of convalescent plasma in the treatment of COVID-19. | |
|---|---|
| Inclusion Criteria | 1. Hospitalized for PCR confirmed COVID-19,<br>2. Patient at least 18 years of age,<br>3. Patient or POA willing and able to provide verbal consent (or may use two-physician concurrence if POA unavailable),<br>4. Early mild to moderate disease:<br>• Duration of symptoms < 7 days<br>▪ Does not require supplemental oxygen (i.e. do not meet criteria for dexamethasone) |
| Exclusion Criteria | 1. Patients in terminal stage of disease<br>2. Female with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed<br>3. Receipt of pooled immunoglobulin in past 30 days<br>4. Known IgA deficiency<br>5. Contraindications to transfusion, possibly including a history of prior life-threatening allergic reactions to transfusion of blood products<br>6. Clinical evidence (in the judgment of site investigator) that etiology of illness is not primarily COVID-19 related<br>7. 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 |

[1] Simonovich V et al. A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia. N Engl J Med. 2020. DOI:

[2] Agarwal A et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: open lable phase II multicenter randomized controlled trial (PLACID). BMI 2020;371. doi: https://doi.org/10.1136/bmj.m3939

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

While some subgroups may benefit from the administration of convalescent plasma, recent prospective randomized controlled trials have not shown clear benefit with its administration for hospitalized patients with severe COVID-19.[1,2] Could be considered in case-by case basis in mild to moderate illness. If considered, recommended criteria are listed below:




[1] Simonovich V et al. A Randomized Trial of Convalescent Plasma in COVID-19 Severe Pneumonia. N Engl J Med. 2020. DOI:

[2] Agarwal A et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: open lable phase II multicenter randomized controlled trial (PLACID). BMI 2020;371. doi: https://doi.org/10.1136/bmj.m3939

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

The below adult criteria are recommendations for use and are not intended to be finite restrictions. Providers may use the clinical judgment in treating patients with Remdesivir for patients that do not meet the below criteria. Contact Derek Vander Horst (SHGR Pharmacy) or Infectious Diseases on call if any questions.

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.

| | **Adult Patients (≥18 years of age)** | **Pediatric Patients (<18 years of age)** |
|---|---|---|
| Inclusion Criteria | 1. Hospitalized for PCR confirmed COVID-19,<br>2. At least 18 years of age,<br>3. At least 40kg actual body weight,<br>4. Duration of symptoms ≤ 10 days,<br>5. LFTs < 10X upper limit of normal,<br>6. Clinical criteria:<br>○ Acute respiratory failure requiring ventilatory support /ECMO for less than 24 hours<br>○ 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) | 1. Hospitalized for PCR confirmed COVID-19,<br>2. Less than 18 years of age,<br>3. New or increasing oxygen requirement or respiratory compromise,<br>4. Diagnosis of MIS-C |
| Exclusion Criteria | • Hypersensitivity to any component of Remdesivir<br>• Current presentation not primarily related to COVID-19 as per treating physician judgement<br><br>Note: Not routinely recommended for eGFR < 30 mL/min or dialysis. Appropriate dosing scheme for hemodialysis (HD, CRRT, PIRRT) remains unknown. | • 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<br>• ALT or AST > 5 ULN<br>• eGFR < 30 mL/min/1.73m2 using Schwartz formula for participants ≥ 1 year of age OR elevation in creatinine<br>• If < 28 days of age, any major congenital renal anomaly<br>• If < 24 hours of age, Apgar score < 5 when last recorded<br>• Known hypersensitivity to the study drug, the metabolites, or formulation excipient<br>• Positive pregnancy test at screening only for female of childbearing potential |

**Table 5 – Suggested Criteria for Treatment of Hospitalized Patients COVID-19 with Tocilizumab**

The below adult criteria are recommendations for use of Tocilizumab in hospitalized adults with COVID-19. Click here for additional detail regarding dosing and recommended monitoring labs. Contact Immunology or Infectious Diseases on call if any questions.

- Hospitalized for PCR confirmed COVID-19,
- At least 18 years of age,
- LFTs < 5X upper limit of normal,
- Clinical criteria (either one of the below):
    a. Patients admitted to the ICU within the last 24 hours for acute respiratory failure requiring mechanical ventilation and/or ECMO
    b. Any patients with rapidly increasing oxygen needs requiring high flow nasal canula (> 0.4 $FiO_2$/30 L/min) or non-invasive mechanical ventilation **AND** have elevated inflammatory markers (CRP, Ferritin, D-dimer, etc.)
        i. Note: RECOVERY Trial used CRP ≥ 75 mg/L

- Hypersensitivity to any component of Tocilizumab
- Current presentation not primarily related to COVID-19 as per treating physician judgement
- LFTs ≥ 5X upper limit of normal
- High risk for GI perforation
- Current uncontrolled non-COVID-19 infection (i.e. bacterial, fungal, non-SARS-CoV2 viral)
- Absolute neutrophil count < 500 or significant immunosuppression
- Platelet count < 50,000 cells/ uL
- Pregnancy & Pediatrics – Contact Immunology prior to use

| Therapeutic Agent & Mechanism | Data on Use | Dosing Strategies | Duration of Therapy | Renal Dosing | Monitoring/Considerations |
|---|---|---|---|---|---|
| **Remdesivir:** nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase | Inhibits SARS-CoV-2 in vitro[1]<br><br>Remdesivir has not shown definitive mortality benefit for the treatment of COVID19[2]<br><br>Remdesivir may shorten duration of symptoms and length of stay in hospitalized patients with COVID19[2]<br><br>The benefit in patients with symptoms greater than 10 days is unclear | Pediatric<br>< 40 kg: 5 mg/kg per dose IV once daily on day 1, followed by 2.5 mg/kg per dose IV once daily<br>> 40 kg: 200 mg IV once daily on day 1, followed by 100 mg IV once daily<br><br>Adult<br>200 mg IV once daily on day 1, followed by 100 mg IV once daily | 5 days | 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[3]<br><br>The dosing of Remdesivir in any dialysis modality is unknown | Major Adverse Events:<br>• Hepatic toxicity<br>• Infusion related reactions (hypotension, fever)<br>• Mild-moderate rash<br><br>Monitoring:<br>• 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.

[3] Thakare S et al. Safety of Remdesivir in patients with acute or chronic kidney disease. Kidney Int Rep. Oct 2020. DOI: 10.1016/j.ekir.2020.10.005

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| **Tocilizumab:** IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients | Tocilizumab is recommended for hospitalized adults with COVID-19 that are rapidly declining with elevated inflammatory markers requiring mechanical intubation, ECMO, or HFNC.[6,7,8,9,10]<br><br>When used in this fashion, as a single dose, Tocilizumab was able to showcase mortality benefit for the critically ill COVID-19 population.<br><br>Contact SHMG Allergy & Immunology with questions | Adult<br>40-59 kg: 400 mg IV<br>60-84 kg: 600 mg IV<br>≥85 kg: 800 mg IV<br><br>Use actual body weight, rounded to nearest 200mg<br>Max dose = 800 mg | One dose | No dose adjustment for renal or hepatic disease | REMS Program for CAR-T, pharmacy **must** always maintain stock.<br><br>Major Adverse Events:<br>• Hepatic toxicity<br><br>Monitoring:<br>• Tb QuantiFERON<br>• LFTs<br>• CBC<br><br>Contraindications:<br>• Active Tb<br><br>NOTE: Screening for Tb is no longer recommended with single dose of Tocilizumab for COVID-19 |

[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
[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.
[10] Horby et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomized, controlled, open-label, platform trial. Feb 2021. Available here: https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

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| **Baricitinib:** janus kinase (JAK) enzyme inhibitor, currently approved for rheumatoid arthritis | Given EUA by the FDA to be given in combination with Remdesivir for hospitalized patients with COVID-19<br><br>The combination of Baricitinib and Remdesivir decreased the median time to a composite endpoint of hospital discharge or improvement by approximately one day.<br><br>The combination of Dexamethasone with Baricitinib remains unstudied and carries inherent risk of immunosuppression | 4mg by mouth once daily in combination with Remdesivir | 14 days or hospital discharge; whichever sooner | Baricitinib requires adjustment renal dysfunction, lymphopenia, and neutropenia | Given significant drug-drug interactions, monitoring, and risk of toxicity it is felt that the risks of Baricitinib outweigh the benefit for use in COVID-19 at this time.<br><br>We do not currently recommend use of Baricitinib as approved by FDA EUA and it is currently unavailable to prescribe. |

**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