
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>
<thead>
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<th>Decision Pathway</th>
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<tr>
<td>Hospitalized patient with confirmed COVID-19</td>
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<tr>
<td>Baseline Orders – See Table 1</td>
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<td>Adult Admission</td>
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<td>Review Treatment Pearls (Table 2) and Special Populations (Table 3)</td>
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<td><strong>NOTE:</strong> ID consultation is recommended for immunocompromised patients</td>
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<tr>
<td>Evaluate for convalescent plasma – See Table 4</td>
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<tr>
<td>Consent instructions here</td>
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<tr>
<td>Evaluate for Remdesivir – See Table 5</td>
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<tr>
<td>Consult ID for evaluation in patients that meet criteria</td>
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<tr>
<td><strong>NOTE:</strong> There are currently insufficient data to recommend the use of hydroxychloroquine for COVID-19. Risks likely outweigh the benefits</td>
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<tr>
<td>Repeat daily labs – See Table 1</td>
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<tr>
<td>Immunology will follow daily labs to help guide ordering of tocilizumab or anakinra</td>
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<tr>
<td>Immunology will contact the attending physician to discuss and order appropriate agent</td>
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<tr>
<td>Pediatric Admission (&lt; 18 years)</td>
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<tr>
<td>Consider Pediatric ID consultation for pediatrics – See Table 3</td>
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<tr>
<td>Evaluate for compassionate use Remdesivir</td>
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<tr>
<td>If enrolled to receive Remdesivir, not candidate for other experimental therapies. Discontinue daily immunotherapy labs.</td>
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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 be 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

NOTE: CT scans are not diagnostic for COVID-19, and should be ordered only if results will change patient management

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**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. Systemic corticosteroids should not be routinely used in the treatment of COVID-19. Inhaled corticosteroids should be discontinued if possible. See the last page of this guideline for more information.
3. In the setting of ARDS, BiPAP is unlikely to be useful. Consider intubation early in COVID positive patients with worsening respiratory failure.
4. 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.
5. Low tidal volume vent and high PEEP (data suggests lot of patients have diffuse GGO but higher compliance)
6. Many COVID patients benefit from proning, and may benefit from long periods of proning (18 -22 hours).
8. There is insufficient evidence to support the routine addition of azithromycin to hydroxychloroquine for the experimental treatment of COVID-19.
9. Routine ID consultation is not required for mild-moderate cases. If lack of clinical improvement, consider ID consultation. All cases of COVID-19 treated with pharmacologic therapy will be reviewed by SH Adult & Pediatric Antimicrobial Stewardship Program for appropriateness.
<table>
<thead>
<tr>
<th>Special Population</th>
<th>Treatment Recommendations</th>
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| **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 **not** 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. |
| **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  
  • 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**           | • 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. |
| **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 |
Figure 2- Individual Use of Convalescent Plasma for The Treatment of PCR Confirmed COVID-19

Hospitalized patient with confirmed COVID-19

Assess Inclusion/Exclusion Criteria – See Table 4

PerfectServe “COVID-19 Research” regarding patient inquiry on the use of convalescent plasma

Attending Physician Obtain Consent: Instructions for obtaining consent are available here

Attending physician to order ABO Screening

EPIC Order for transfusion will be placed by Dr. Simeunovic

Transfusion per SH Transfusion Protocol with appropriate monitoring
Table 4 – 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 | 1. Hospitalized for PCR confirmed COVID-19,  
|                   | 2. Patient at least 18 years of age,  
|                   | 3. Patient or POA willing and able to provide written informed consent,  
|                   | 4. Meets criteria for:  
|                   |   ○ Severe illness with potential for progression to life threatening disease defined as:  
|                   |     ▪ Dyspnea  
|                   |     ▪ Respiratory rate ≥ 30 breaths per minute  
|                   |     ▪ O2 saturation ≤ 93%  
|                   |     ▪ PaO2/FiO2 ratio < 300  
|                   |     ▪ Lung infiltrates progression > 50% in 24-48 hours  
|                   |   OR  
|                   |     ○ Life threatening disease defined as:  
|                   |       ▪ Respiratory failure  
|                   |       ▪ Septic shock  
|                   |       ▪ Multisystem organ failure  

| Exclusion Criteria | • Greater than 14 days since onset of COVID-19 symptoms  
|                   | • Patients in terminal stage of disease  
|                   | • Female with positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period  
|                   | • Receipt of pooled immunoglobulin in past 30 days  
|                   | • Known IgA deficiency  
|                   | • Contraindications to transfusion, possibly including a history of prior life-threatening allergic reactions to transfusion of blood products  
|                   | • Clinical evidence (in the judgment of site investigator) that etiology of illness is not primarily COVID-19 related  
|                   | • 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 5 – Treatment of COVID-19 with Remdesivir via FDA Emergency Use Authorization
Contact Derek Vander Horst (SHGR Pharmacy) for all questions regarding the use of Remdesivir in the treatment of COVID-19.

| Inclusion Criteria | 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. eGFR >30 mL/min,  
|                   | 6. LFTs < 5X upper limit of normal,  

7. **Clinical criteria:**
   - Acute respiratory failure requiring ventilatory support /ECMO
   - Severe disease (SpO2 < 93% on room air and pulmonary infiltrates on imaging), with risk for progression to intubation (immunosuppression, chronic lung disease, morbid obesity, uncontrolled DM with HgA1C >8)

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>• Hypersensitivity to any component of Remdesivir</td>
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<tr>
<td>• Terminal stage of the disease</td>
</tr>
<tr>
<td>• Current presentation not primarily related to COVID-19 as per treating physician judgement</td>
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<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>
</table>
| **Remdesivir:** nucleoside inhibitor with broad antiviral activity; inhibits viral RNA synthesis by polymerase | Inhibits SARS-CoV-2 in vitro<sup>1</sup> 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
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 by FDA EUA or via compassionate use from Gilead. | 5 or 10 days | Patients with renal/hepatic dysfunction or dialysis are excluded from compassion use and clinical trials. | Compassionate use available only or pediatrics (Age < 18) or pregnant women.
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 |

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<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
Table 6 – Criteria for Use of Immunomodulating Therapy (Only to be ordered under direction from SHMG Allergy & Immunology)
Contact Dr. Nick Hartog for all questions regarding the use of immunomodulators in the treatment of COVID-19.

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hospitalized for PCR confirmed COVID-19,</td>
<td>• Metastatic CA</td>
</tr>
<tr>
<td>• Worsening respiratory status in last 24 hours and on ≥4L NC or intubated (for adults)</td>
<td>• DNI or where escalation of care would not be pursued based on goals of care</td>
</tr>
<tr>
<td>• &lt;14 days into current illness (if duration is noted)</td>
<td>• LVEF &lt; 30%</td>
</tr>
<tr>
<td>• Assessment by SHMG Allergy &amp; Immunology</td>
<td>• CKD on dialysis at baseline</td>
</tr>
<tr>
<td>• Cardiac arrest in hospital</td>
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**Tocilizumab:** IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients

Under the direction of Adult Infectious Diseases or Allergy & Immunology

<table>
<thead>
<tr>
<th>Tocilizumab: IL-6 inhibitor currently approved for cytokine storm in CAR-T cell patients</th>
<th>Spectrum Health Use Criteria: SHMG Immunology will be reviewing all cases of COVID-19 and recommending therapy. Contact Dr. Nicholas Hartog with any questions.</th>
<th>Pediatric</th>
<th>Under direction of SHMG Allergy &amp; Immunology</th>
<th>No dose adjustment for renal or hepatic disease</th>
<th>REMS Program for CAR-T, pharmacy must always maintain stock.</th>
</tr>
</thead>
</table>
| Small report of 21 patients with severe hypoxia and intubation showed possible improvement of respiratory function following therapy | <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 | Under direction of SHMG Allergy & Immunology | No dose adjustment for renal or hepatic disease | REMS Program for CAR-T, pharmacy must always maintain stock. |
| | | Major Adverse Events:  
• Hepatic toxicity  
Monitoring – Labs to be discussed with Immunology and obtained (but do not need to have resulted) prior to administration.  
• Tb  
• QuantiFERON  
• LFTs  
• CBC |
Doses may be repeated up to every 8 hours for max of 3 doses over 24 hours

Contraindications:
- Active Tb

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**Anakinra**: IL-1 receptor antagonist

**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

**Adult**: 100mg per day SQ, can consider increase to twice daily if no response

**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**: Tb QuantiFERON, CBC

**Contraindications**: Active Tb

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**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

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*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*
• Chloroquine - Due to lack of in vivo safety & efficacy data, Spectrum Health does not recommend the use of chloroquine for 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.

• 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.

\(^7\)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