Currently there is no FDA approved antiviral therapy for SARS-CoV-2 infection. The mainstay of therapy is supportive care. The treatment algorithm presented here is based on a review of currently available literature, particularly the NIH and IDSA published treatment guidelines. On May 1, 2020 the FDA issued an Emergency Use Authorization (EUA) for use of Remdesivir for the treatment of hospitalized COVID-19 patients. The EUA was revised August 28, 2020. The treatment algorithm is based on the NIH guidelines, most recently updated 10/9/20, and will be updated to reflect new data as it becomes available.

**COVID-19 patient**

- **Outpatient**
  - Supportive care

- **Inpatient admission, including pregnant women**
  - **SpO2 > 94%**
    - Supportive care
  - **SpO2 ≤ 94%**
    - Dexamethasone
    - Evaluate for eligibility for remdesivir
      - **Not eligible**
        - Supportive care
      - **Eligible**
        - Consult Infectious Diseases

1. Clinical symptoms + positive pcr test
2. Dexamethasone 6mg daily x 10 days or until hospital discharge, whichever is shorter.
3. If remdesivir was initiated at another VT hospital, the remaining doses should be transported with the patient for continuation of therapy. Confirm ongoing eligibility (table 2).
4. Remdesivir criteria of use: Positive COVID-19 pcr test, O2 sat ≤ 94%, CrCl ≥ 30 ml/min, AST & ALT < 5x ULN, use of IV medication is clinically appropriate.
5. See table 1 for information about remdesivir
6. See table 2 for information about remdesivir consent and monitoring.
7. See table 3 for information about anti-inflammatory agents, criteria of use, and exclusion criteria.
Remdesivir is an investigational nucleotide analog with antiviral activity. It is infused as an adenosine nucleotide prodrug, then metabolized to its pharmacologically active form of nucleoside triphosphate metabolite. It acts as an analog of adenosine triphosphate (ATP) to compete with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during replication of viral RNA. Remdesivir is not FDA approved.

### Supply Source & Formulation

<table>
<thead>
<tr>
<th>Donated supply from US Government</th>
<th>Dosing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>For adult patients, solution formulation is preferred as children &lt;40kg can only receive the lyophilized powder formulation.</td>
<td>200 mg IV on day 1, then 100 mg IV daily for up to 4 days or hospital discharge, whichever comes first.</td>
<td>Infectious Diseases consult required.</td>
</tr>
<tr>
<td>Therapy can be extended up to 10 days if no substantial clinical improvement is seen at day 5.</td>
<td>Remdesivir is currently available in limited supply through an FDA Emergency Use Authorization (EUA) letter. The EUA was revised on August 28, 2020. The major revision is to include expand eligibility of remdesivir to hospitalized patients not needing supplemental oxygen. This decision was based on this study published in JAMA. The study concludes that patients who received 5 days of remdesivir had a statistically significant difference in clinical status (favorable) compared to standard of care or 10 days of remdesivir at 11 days of care. The authors state that they are uncertain of the clinical importance of these findings. Due to the limited supply of remdesivir, UVMCC will continue to follow the previously agreed upon clinical criteria by the VT CMO group of initiation of remdesivir for patients who have O₂ sat ≤ 94% on ambient air.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Current criteria for consideration of use as decided by the State of Vermont: Positive COVID-19 test O₂ sat ≤ 94%, or the need for supplemental O₂, mechanical ventilation, or ECMO CrCl ≥ 30ml/min AST &amp; ALT ≤ 5x upper limit of normal The use of IV medication is appropriate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remdesivir should not be co-administered with strong inducers of CYP450, such as rifampin. Check for drug-drug interactions prior to prescribing. Concomitant use of hydroxychloroquine, chloroquine, and remdesivir is not recommended.</td>
<td></td>
</tr>
</tbody>
</table>

### Gilead Compassionate Use Program

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Dosing</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women: 200 mg IV on day 1, then 100 mg IV daily for up to 4 days or hospital discharge, whichever comes first.</td>
<td>Therapy can be extended up to 10 days if no substantial clinical improvement is seen at day 5.</td>
<td>Infectious Diseases consult required.</td>
</tr>
<tr>
<td></td>
<td>Currently, Gilead prefers pregnant women in need of antiviral therapy access Remdesivir through the compassionate use access program over the US government donated supply. The EUA stipulates that the lyophilized powder formulation of remdesivir should be used for children weighing 3.5kg – 40kg. There is limited supply of the lyophilized powder formulation in Vermont. If this supply is exhausted and not replaced by the US Government, further supply should be obtained through Gilead’s compassionate use program. Remdesivir can be obtained through Gilead’s compassionate use program.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><a href="https://rdvcu.gilead.com/">https://rdvcu.gilead.com/</a></td>
<td>Obtaining compassionate use remdesivir requires assistance by the investigational pharmacy and UVM IRB.</td>
</tr>
</tbody>
</table>

### Table 1. Remdesivir Drug Information

Remdesivir is an investigational nucleotide analog with antiviral activity. It is infused as an adenosine nucleotide prodrug, then metabolized to its pharmacologically active form of nucleoside triphosphate metabolite. It acts as an analog of adenosine triphosphate (ATP) to compete with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, resulting in delayed chain termination during replication of viral RNA. Remdesivir is not FDA approved.

## Consent

Current criteria for consideration of use as decided by the State of Vermont:
- Positive COVID-19 pcr test
- $O_2$ sat ≤ 94%, or the need for supplemental $O_2$, mechanical ventilation, or ECMO
- $CrCl ≥ 30$ml/min
- $AST & ALT ≤ 5x$ upper limit of normal

The use of IV medication is appropriate

Prior to administration:
1. It must be documented that the patient (or caregiver) received the EUA patient fact sheet and fact sheet has been explained to the patient. The patient fact sheet has been translated into eight languages as all are available on the UVMMC COVID-19 website.
2. Physician must document that he/she has read the EUA physician fact sheet.
3. It must be documented that the patient has been informed about alternative treatments.
4. It must be documented that the patient has been informed that remdesivir is not an FDA approved medication.

Use dotphrase ".remdesivirconsent" in H&P or progress note to document patient consent.

## Monitoring

Daily laboratory monitoring:
- Creatinine and creatinine clearance
- AST, ALT
- CBC
- Electrolytes

Risk of infusion related reaction:
Infusion-related reactions have been observed during, and/or been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitive to remdesivir.

Discontinue remdesivir if $ALT ≥ 5x$ upper limit of normal. Remdesivir may be restarted when $ALT ≤ 5x$ upper limit of normal. Discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

Adverse Events or death must be reported to FDA Medwatch within 7 days of event. [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm) and copied to Gilead at Safety_fc@gilead.com

Serious adverse events are defined in the EUA are:
- Death
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly

This document is subject to change. Updated by the UVMMC COVID-19 Therapeutics Working Group on X/X/2020.
### Table 3. Anti-inflammatory Agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosing</th>
<th>Notes</th>
<th>Criteria for consideration of use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>6mg po or IV daily x for up to 10 days, or until hospital discharge, whichever comes first</td>
<td>The UK Recovery Trial found that patients with COVID-19 and required supplemental O2, who received dexamethasone 6mg daily x 5-10 days had reduced 28 day mortality compared to those patients who did not need supplemental oxygen therapy. This study prompted the IDSA and NIH to include dexamethasone in their treatment recommendations. This study is awaiting the peer-review process and publication. Oral dexamethasone is the preferred agent for patients not intubated or receiving positive pressure ventilation. Dexamethasone 6mg = methylprednisolone 32mg = prednisone 40mg.</td>
<td>Indication for prescribing: Positive COVID-19 pcr test O2 ≤ 94% on ambient air</td>
</tr>
<tr>
<td><strong>Baricitinib</strong></td>
<td>if CrCl &gt; 60ml/min 4mg po daily x 7 days</td>
<td>Rheumatology approval required. Baricitinib inhibits Janus kinase (JAK) enzymes, which are involved in stimulating hematopoiesis and immune cell function through a complex signaling pathway. Its role in the treatment of COVID-19 is evolving. The current thought is early administration of baricitinib could stave off cytokine storm. Currently NIH guideline does not support the use of baricitinib outside of a clinical trial due to lack of data. The Adaptive COVID-19 Treatment Trial (ACTT-2) published in September 2020 showed that baricitinib + remdesivir decreased median recovery time by 1 day compared to remdesivir alone. If tablet cannot be swallowed, medication can be dispersed in a small amount of liquid.</td>
<td>Inclusion criteria: Positive COVID-19 pcr test Fever Radiographic evidence of pneumonia O2 &lt; 94% on ambient air Exclusion criteria: Pregnant or breast feeding Already taking a JAKi or other biologic DMARD, anti-IL6 or anti-IL8 antibodies, or potent immunosuppressants, such as azathioprine and cyclosporine AST/ALT &gt; 5x ULN Absolute lymphocyte count &lt;500 cells/mL Absolute neutrophil count &lt;1,000 cells/mL Hemoglobin &lt;8g/dL Platelets &lt; 50,000/mL CrCl &lt; 30ml/min Malignancy and receiving immunosuppressant therapy Active or suspected bacterial or fungal, or viral infection other than SARS-CoV-2 Symptoms of or known diagnosis of thromboembolism, phelebitis, or hypercoagulable state</td>
</tr>
<tr>
<td><strong>Tocilizumab</strong></td>
<td>400mg IV x1 (Use order panel)</td>
<td>The use of tocilizumab outside of a clinical trial is not endorsed by the IDSA or NIH due to lack of data showing benefit. Rheumatology approval required. Call Rheumatology if patient has progressive respiratory decline with need for higher level of respiratory support, or needing transfer to the ICU. Tocilizumab is an interleukin-6 (IL-6) receptor inhibitor, binding to soluble and membrane-bound IL-6 receptors. It is currently under investigation as an agent targeting cytokine storm as a result of COVID-19. Tocilizumab has been shown to be safe in pregnancy.</td>
<td>Contraindications: any known hypersensitivity to tocilizumab. Inclusion criteria: Positive COVID-19 pcr test Worsening respiratory decline with impending transfer to the ICU Onset of symptoms less than 1 week and hospitalization &lt;48 hours Temperature &gt; 38.3 C Labs • Ferritin &gt; 1000 ng/mL • D-Dimer &gt;1000 ng/mL • LDH &gt;250 U/L • CRP &gt; 70 mg/L or &gt;40 mg/L and doubling within 48 hours • Lymphocyte count &lt; 0.6 x 10^9/L • Likelihood of good clinical outcome based on age and other comorbidities</td>
</tr>
</tbody>
</table>