UW Medicine Treatment Guidelines for SARS-CoV-2 Infection/COVID-19

There are no FDA-approved therapies for treatment of SARS-CoV-2. Clinical trial data is rapidly emerging and national guidelines addressing treatment options and evaluating clinical data have been published by the National Institutes of Health. The National Guidelines will be frequently updated to incorporate new information to guide therapies. The UW Medicine Treatment Guidelines will address institution specific practices, including availability of clinical trials.

Our best opportunity to understand how to treat COVID-19 is to study stepwise interventions and compare findings to the current best available standard. When available, clinical trials are recommended.

Please call the ID team with questions about inpatient management of specific patients and refer to national published guidelines for recommendations.

<table>
<thead>
<tr>
<th>Patient population with COVID-19</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>Consider clinical trial enrollment.</td>
</tr>
<tr>
<td></td>
<td>UW-Virology Research Clinic: <a href="https://depts.washington.edu/covid19trx/COVIDTreatment@uw.edu">https://depts.washington.edu/covid19trx/COVIDTreatment@uw.edu</a></td>
</tr>
<tr>
<td>Lower Respiratory Tract infection (LRTI)</td>
<td>Recommend IV Remdesivir; use link for approval: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a></td>
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<tr>
<td></td>
<td>Consider clinical trial enrollment.</td>
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<td></td>
<td>UWMC/NWH: Ruxolitinib (RUX-COVID) <a href="mailto:actucovidstudies@uw.edu">actucovidstudies@uw.edu</a></td>
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<tr>
<td></td>
<td>Convalescent plasma is available thru transfusion services.</td>
</tr>
<tr>
<td>LRTI with mechanical ventilation</td>
<td>Recommend IV Remdesivir; Use link for approval: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a></td>
</tr>
<tr>
<td></td>
<td>Convalescent plasma is available thru transfusion services.</td>
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<tr>
<td>Post-exposure prophylaxis</td>
<td>Contact Study Team <a href="https://depts.washington.edu/covid19pep/covid19pep@uw.edu">https://depts.washington.edu/covid19pep/covid19pep@uw.edu</a></td>
</tr>
<tr>
<td>Pregnant patients with LRTI</td>
<td>Recommend IV Remdesivir: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a></td>
</tr>
</tbody>
</table>
**Recommended Agents and Available Clinical Trials**

**IV REMDESIVIR**

**Mechanism of Action:** nucleotide analogue, initially developed for treatment of Ebola. Works by inhibiting RNA-dependent RNA polymerase.

**Evidence Summary:** *In-vitro* activity against MERS and SARS, has shown efficacy in animal models\(^1\)-\(^3\). Remdesivir inhibits SARS-CoV-2 *in vitro*\(^4\).

Hospitalized patients with COVID-19 lower-tract disease who received remdesivir recovered faster than similar patients who received placebo in an NIH trial of 1063 people. The trial (known as the Adaptive COVID-19 Treatment Trial, or ACTT), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, is the first randomized clinical trial launched in the United States to evaluate an experimental treatment for COVID-19\(^5\). Adult patients hospitalized with lower respiratory tract disease were randomized to either IV Remdesivir for 10 days or placebo. The primary endpoint was time to recovery, defined by either discharge from hospital or hospitalization for infection control purposes only.

Interim results of enrolled patients (n=1063) indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (p<0.001). Specifically, the median time to recovery was 11 days (95% CI, 9 to 12) for patients treated with remdesivir compared with 15 days (95% CI, 13 to 19) for those who received placebo. Results suggested a trend toward improved survival, with a mortality rate of 7.1% for the group receiving remdesivir versus 11.9% for the placebo group (Hazard Ratio for death 0.70; 95% CI, 0.47 to 1.04).

The optimal duration of IV Remdesivir was evaluated in 397 patients hospitalized with COVID-19\(^6\). Patients were randomized to either receive 5 or 10 days of IV remdesivir; there was no placebo group in this study. The groups had similar demographics but not baseline diseases characteristics. A greater proportion of patients in the 10 day group were in the two most severe disease groups. Most of the patients were receiving noninvasive ventilation or high-flow oxygen or receiving low-flow supplemental oxygen at baseline. The primary endpoint was clinical status on day 14, assessed by a 7-point ordinal scale. After adjustment for baseline clinical status, patients in the 10-day group had a distribution in clinical status at day 14 that was similar to patients in the 5-day group (P=0.14). Few patients were mechanically ventilated in this study so the duration for this population requires further study.

**Based on the above data, the FDA has authorized Remdesivir for Emergency Use**\(^7\). This drug is not FDA approved but will be available on a limited basis at UW Medicine. IV Remdesivir can be accessed by submitting a request through redcap ([https://redcap.link/remdesivirEUA_UW](https://redcap.link/remdesivirEUA_UW)).

**Compassionate use remdesivir is also available for hospitalized pediatric patients.**
### Table 2. Available Mechanisms to Obtain Remdesivir at UW Medicine

<table>
<thead>
<tr>
<th>Target population</th>
<th>Precautions</th>
<th>Informed Consent</th>
<th>Availability and Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Use Authorization</td>
<td>Hospitalized patients (including pregnant women) with confirmed SARS-CoV-2 by PCR AND severe disease defined as patients with oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).</td>
<td>1) ALT levels &gt; 5x ULN 2) eGFR &lt;30 mL/min or dialysis or continuous veno-venous hemofiltration</td>
<td>No Provide “FDA Fact Sheet” to patient or family members</td>
</tr>
</tbody>
</table>

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<tr>
<th>Inclusion Criteria</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Compassionate Use</td>
<td>Hospitalized children &lt;18 yo with confirmed COVID-19 and severe manifestation of disease</td>
</tr>
</tbody>
</table>

**Emergency Authorization Use**

To submit request: [https://redcap.link/remdesivirEUA_UW](https://redcap.link/remdesivirEUA_UW)

To request IV Remdesivir for patients meeting the definition of severe disease, complete the survey by clicking on the link above. You will be asked to enter your contact information, the patient’s age and clinical information to the secure form with no other patient identifying information to avoid potential bias. Requests will be reviewed by the Remdesivir Clinical Allocation Team and decisions will be made within 24 hours based on the prognosis and likelihood of benefit as reflected by the clinical information as well as drug availability.

**Criteria for Remdesivir EUA by FDA:**

- Hospitalized pt with suspected or laboratory confirmed SARS-COV2 (PCR) with severe disease;
- Severe disease is defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO);
- Pregnant patients are eligible but risks and benefits need to be addressed
- See: [https://www.fda.gov/media/137566/download](https://www.fda.gov/media/137566/download)
Precaution:
- GFR ≤30 ml/min (calculated by eGFR; value auto-calculated and shown for all serum creatinine in ORCA)
- Contraindicated in patients with known hypersensitivity to remdesivir
- Baseline ALT ≥5 ULN

Dosing:
200 mg IV x 1 on Day 1, followed by 100 mg IV daily for 5-10 days

Duration:
- Hospitalized patients requiring supplemental oxygen but not requiring mechanical ventilation: A 5 day course of remdesivir will be prescribed to patients. The course can be continued up to 10 days if patient does not demonstrate improvement.
- For patients who are mechanically ventilated or patients on ECMO, therapy can be extended to 10 days

Suggested Monitoring:
- Daily CBC, Chemistries, and Liver enzymes
- If GFR < 30 ml/min or ALT > 5 x ULN, stop medication. Remdesivir may be restarted when ALT is < 5 times the upper limit of normal

Regulatory requirements:
- Provide patient or patient family with “Fact Sheet for Patients provided by the FDA.”
  https://www.fda.gov/media/137565/download
- Inform of alternatives to receiving remdesivir
- Informed that remdesivir is an unapproved drug that is authorized for use under EUA.
- Mandatory reporting of all medication errors and adverse events (death, serious adverse events*) considered to be potentially related to remdesivir occurring during remdesivir treatment within 7 calendar days from the onset of the event.
- The reports should include unique identifiers and the words “Remdesivir under Emergency Use Authorization (EUA)” in the description section of the report.
- Submit adverse event reports to FDA Med Watch using one of the following methods:
  - Complete and submit the report online www.fda.gov/medwatch/report.htm

Use in Pregnancy: All the Remdesivir trials listed above excluded pregnant and breastfeeding individuals including the ACTT-1 trial. Pregnant women were included in the Ebola Virus Disease trial which included Remdesivir®. 6.1% (17/277) of women enrolled were pregnant at the time of EVD diagnosis: of whom 6/77 (7.8%) were randomized to Remdesivir. In the severe adverse event (SAE) supplemental material there were no maternal, pregnancy or neonatal related SAE noted in the Remdesivir group.

Toxicities and Drug Metabolism: Elevated transaminases, reversible kidney injury, hypotension during infusion.

Compassionate Use: https://rdvcu.gilead.com/ Requests are ONLY for children less than 18 years of age with confirmed COVID-19 and severe manifestations of disease.
Emerging Therapies:

Dexamethasone:

The RECOVERY (Randomised Evaluation of COVID-19 thERapY) trial has enrolled over 11,500 inpatients with COVID-19 infection from over 176 hospitals in the UK. Participants are randomized to standard of care, low-dose dexamethasone, hydroxychloroquine, lopinavir-ritonavir, and azithromycin. Simultaneously, participants are randomized to standard of care vs. convalescent plasma. Patients who decompensate clinically may also be randomized to placebo vs. tocilizumab. Preliminary results for the dexamethasone arm were released on 6/16/2020.

A total of 2104 patients were randomized to dexamethasone 6 mg daily for 10 days and compared to 4321 patients who received standard care. Among those with standard care, 28-day mortality was 41% among those requiring mechanical ventilation, 25% among those who received oxygen alone, and 13% among those not requiring respiratory intervention. Dexamethasone significantly reduced deaths among patients receiving ventilation (Rate Ratio (RR)=0.65, 95% CI=0.48-0.88) and among those receiving oxygen only (RR=0.80, 95% CI=0.67-0.96). No benefit was seen among persons who did not require oxygen therapy (RR=1.22, 95% CI=0.86-1.75).

More information about preliminary dexamethasone results from the RECOVERY team is available.\footnote{9}


Several other therapies are currently being studied for treatment of COVID-19. These therapies are not currently recommended for use in patients, pending further data from clinical trials. Further information about these agents and the rationale for considering their use is available at NIH COVID-19 Guidelines (https://www.covid19treatmentguidelines.nih.gov/).
Clinical Trials Available at UW Medicine

Inpatient Studies

The RUX-COVID clinical trial (NCT04362137) is available at UWMC-ML and NW. Ruxolitonib is a JAK1/JAK2 inhibitor which is approved for GVHD, Polycythemia Vera, and myelofibrosis. Off label use for CAR-T associated cytokine storm and other cytokine release syndromes, such as HLH. Hypothesis is that this is a more holistic immunomodulator that interferes with several processes in the pathway from cytokine syndrome to development of ARDS and may be more potent than blocking a single cytokine.

Contact ACTU COVID Studies hot pager 206 314-8777 or email actuovidstudies@uw.edu for questions or referral of inpatients at either UWMC campus.

Outpatient Studies

The COVID-19 PEP Study (NCT04328961) is a multi-center randomized clinical trial evaluating hydroxychloroquine post-exposure prophylaxis for prevention of SARS-CoV-2 infection. Contact: covid19pep@uw.edu or call/text: 206-520-4366.
For additional information, please visit: https://depts.washington.edu/covid19pep/

The CODID-19 Treatment Study (NCT04354428) is a multi-center randomized clinical trial evaluating hydroxychloroquine alone or in combination with azithromycin to decrease nasal viral shedding and to prevent lower respiratory infection, hospitalization and death in people with early COVID-19 infection. Contact: Covid19Treatment@uw.edu or call/text: 206-520-4366.

For additional information, please visit https://depts.washington.edu/covid19trx/

Both trials are conducted using telemedicine and do not require in person visits.
References


