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 and the Infectious Diseases Society of America. 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 1. Treatment options based on patient population with COVID-19

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td>Consider clinical trial enrollment. For available clinical trials, visit the ITHS website: <a href="https://www.iths.org/iths-covid-19-research-resources/current-covid-19-research/">https://www.iths.org/iths-covid-19-research-resources/current-covid-19-research/</a></td>
</tr>
<tr>
<td><strong>Hospitalized patient with COVID-19 not requiring supplemental oxygen</strong></td>
<td>Recommend against use of Remdesivir Recommend against use of Dexamethasone due to concern for harm.</td>
</tr>
<tr>
<td><strong>Lower Respiratory Tract infection (LRTI), defined as SpO2 &lt; 94% or requiring supplemental oxygen but not mechanically ventilated</strong></td>
<td>Recommend IV Remdesivir; use link to request <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a> Recommend Dexamethasone 6mg daily for up to 10 days; discontinue at discharge. Consider clinical trial enrollment. UWMC/NWH/HMC: Ruxolitinib (RUX-COVID) <a href="mailto:actucovidstudies@uw.edu">actucovidstudies@uw.edu</a>; study pager 206-314-8777 or after hours page through operator “ACTU COVID Studies” Convalescent plasma is available thru transfusion services. Study Coordinator pagers: 206-797-2704 and 206-314-9420</td>
</tr>
<tr>
<td><strong>LRTI with mechanical ventilation</strong></td>
<td>Consider IV Remdesivir; Use link to request: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a> Recommend Dexamethasone 6mg daily for up to 10 days; discontinue at discharge. Convalescent plasma is available thru transfusion services. study coordinator pagers: 206-797-2704 and 206-314-9420</td>
</tr>
<tr>
<td><strong>Post-exposure prophylaxis</strong></td>
<td>Contact Study Team <a href="https://depts.washington.edu/covid19pep/">https://depts.washington.edu/covid19pep/</a> <a href="mailto:covid19pep@uw.edu">covid19pep@uw.edu</a></td>
</tr>
<tr>
<td><strong>Pregnant patients with LRTI</strong></td>
<td>Recommend IV Remdesivir: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a> Consider dexamethasone: Contact Maternal-Fetal Medicine to consider whether dexamethasone is appropriate and whether dose adjustment is indicated for fetal lung maturity.</td>
</tr>
</tbody>
</table>

* Remdesivir was not part of the treatment in the RECOVERY trial; therefore, the safety and efficacy of coadministering remdesivir and dexamethasone are not known.
Recommended Agents and Available Clinical Trials

IV REMDESVIR

**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. Remdesivir inhibits SARS-CoV-2 *in vitro*.

Hospitalized patients with COVID-19 lower-respiratory 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. 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. Patients were randomized to 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 optimal duration for this population requires further study.

In settings where remdesivir supplies are limited, the NIH Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenations (ECMO).

**Based on the above data, the FDA has authorized Remdesivir for Emergency Use.** 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).

Compassionate use remdesivir is also available for hospitalized pediatric patients.
To submit request: 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.
The decision for approval will be sent via email and a text page. If denied, requesting provider will receive an email regarding rationale for denial. Questions can be emailed to remdesivireua@uw.edu. The provider will be expected to send the MRN, complete the paper order form (CPOE order set forthcoming) and complete the regulatory requirements as specified in the email. (i.e. patients must be provided the “FDA fact sheet, etc”) The drug will be sent from the investigational pharmacy.

**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

**Precautions:**
- 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 ALT > 5 x ULN, stop medication. Remdesivir may be restarted when ALT is < 5 times the upper limit of normal

**Regulatory requirements:**

Health care providers must do the following and document in the medical record:
- 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
- Inform 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 MedWatch 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/](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:

Based on preliminary analysis of the data from the RECOVERY trial, both IDSA and NIH issued the following recommendations for use corticosteroids among patients populations:

<table>
<thead>
<tr>
<th>Patient population</th>
<th>NIH</th>
<th>IDSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No supplemental oxygen</td>
<td>Recommends against the use of dexamethasone</td>
<td>Recommends against the use of glucocorticoids (conditional recommendation, low certainty of evidence)</td>
</tr>
<tr>
<td></td>
<td>(A1)</td>
<td>(conditional recommendation, low certainty of evidence)</td>
</tr>
<tr>
<td>Supplemental oxygen but not mechanically ventilated</td>
<td>Dexamethasone is recommended 6mg IV/PO for up to 10 days (B1)</td>
<td>Dexamethasone is recommended at 6mg IV/PO daily (or until discharge if earlier) (conditional recommendations, moderate certainty of evidence)</td>
</tr>
<tr>
<td>Mechanically ventilated</td>
<td>Dexamethasone recommended 6mg IV/PO daily for up to 10 days (A1)</td>
<td>Dexamethasone is recommended at 6mg IV/PO daily (or until discharge if earlier) (conditional recommendations, moderate certainty of evidence)</td>
</tr>
</tbody>
</table>

A1: Strong recommendation for the statement with one or more randomized trials with clinical outcomes and/or validated laboratory endpoints

B1: Moderate recommendation for the statement with one or more randomized trials with clinical outcomes and/or validated laboratory endpoints

The RECOVERY (Randomized Evaluation of COVID-19 thERapY) trial 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, or azithromycin. Simultaneously, participants are randomized to standard of care vs. convalescent plasma. Patients who decompensate clinically may also be randomized to placebo vs. tocilizumab.

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 as 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). Patients with longer duration of symptoms had a greater mortality benefit. Dexamethasone was associated with a reduction in 28 day mortality in patients with symptoms for more than 7 days ((RR: 0.69, 95% CI: 0.63 -0.94))

Considerations:

Before initiating dexamethasone, clinicians should evaluate the patient’s medical history and assess the potential and benefits. Patient may experience hyperglycemia, neurological side effects, adrenal suppression and may be at risk increased bacterial infections. Corticosteroids may increase the risk of reactivation of latent infections (such as hepatitis B, herpesviruses, or tuberculosis).
It is not known whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, will have a similar benefit to dexamethasone. Of note, the dose equivalencies for dexamethasone 6 mg daily are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.

Remdesivir was not part of the treatment in the RECOVERY trial; therefore, the safety and efficacy of coadministering remdesivir and dexamethasone are not known.

**Duration of therapy:**

The duration of the dexamethasone was 6mg IV/PO for up to 10 days (or until discharge if sooner.) The median number of days of therapy was 6 days in the RECOVERY trial, therefore it is not recommended to continue dexamethasone therapy beyond hospitalization.


**Pregnancy:**

Very few pediatric or pregnant patients with COVID-19 were included in the RECOVERY trial; therefore, the safety and efficacy of using dexamethasone in these patients are unknown. Contact Maternal Fetal Medicine for evaluation of pregnant individuals.

If gestational age 23-36 weeks, consider increasing dexamethasone dose to 6mg q12 hours x4 doses to promote fetal lung maturity.

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/) and IDSA Guidelines (https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).
Clinical Trials Available at UW Medicine

Inpatient Studies

The RUX-COVID clinical trial (NCT04362137) is available at UWMC-ML, HMC, and NW. Ruxolitinib 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.

This is a randomized 2:1 double-blinded trial of ruxolitinib vs placebo. Ruxolitinib is an oral pill administered as 5mg BID, which is continued on discharge for 14 days, or can be extended for 28 days if still inpatient and at discretion of study/clinical teams.

Eligibility: Age 18 or older; inpatient status (observation/boarder OK), but not in any critical care unit prior to randomization; pulmonary infiltrate on CXR or Chest CT, RR >30, Requiring supplemental O2, SaO2 of 94% or lower on RA, or P/F <300mmHg

Exclusion: CrCl <30ml/min or Cr >2.0; suspected noncontrolled infection aside from SARS-CoV-2 (superinfecting bacterial PNA ok as long as treated/treatable; admission to the ICU or intubated status; receiving any immunomodulators or anti-rejection meds apart from steroids, women who are pregnant or nursing.

Concomitant use of dexamethasone, remdesivir, or convalescent plasma is permitted per protocol- no other monoclonals allowed.

Contact ACTU COVID Studies hot pager 206 314-8777 or email actucovidstudies@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 COVID-19 PEP trial is conducted using telemedicine and do not require in person visits.
SARS CoV-2 Convalescent Plasma

Mechanism of Action:

The most likely mechanism is viral neutralization by providing anti-SARS CoV-2 neutralizing antibodies in the recipient, or increasing the circulating antibody titer/quality. Other possible mechanisms include antibody-dependent phagocytosis or cytotoxic lymphocyte responses. Antibody-independent (e.g. coagulation factors, albumin) or non-specific immunologic effects are also possible.

Evidence Summary:

Convalescent plasma has been administered since the late 19th century for a variety of infectious and non-infectious entities, most notably including influenza virus (1918, 2009 H1N1 and 2007 H5N1), SARS CoV-112,13 and MERS CoV14,15 infections. An exploratory meta-analysis of these studies suggested that convalescent plasma offered recipients with respiratory viral infections a mortality benefit (OR 0.25, 95% CI 0.14-0.45), which was largely seen when plasma was administered early after symptom onset (<10-14 days) and prior to seroconversion. However, these studies largely lacked control groups and had high risk of bias. Initial experience with convalescent plasma in SARS CoV-2 infection is limited to uncontrolled case series. Shen et al, reported on 5 mechanically-ventilated COVID-19 patients who received convalescent plasma long after symptom onset (10-22 days), all of which subsequently improved clinically. Duan et al. similarly showed improvement in 10 patients (all received plasma, no controls), most of which had moderate-to-high anti-SARS CoV-2 titers prior to receipt of plasma raising the possibility that allogeneic factors independent of neutralizing antibody are involved. A randomized clinical trial of convalescent plasma in addition to standard treatment among 103 patients hospitalized with severe laboratory-confirmed COVID-19 suggested clinical improvement at 28 days among the convalescent plasma group (Hazard Ratio=1.4, p=0.26)19. However, the study was stopped early due to inability to recruit cases and therefore was underpowered to detect a significant difference. Preliminary data from 5000 hospitalized patients with severe COVID-19 infection who received convalescent plasma in the United States as part of the US FDA Expanded Access Program showed few related serious adverse events after transfusion of convalescent plasma, suggesting that convalescent plasma is safe.

Convalescent plasma is available at UW Medicine through Expanded access (Mayo clinic): NCT04338360

For questions regarding ordering of SARS CoV-2 convalescent plasma through the expanded access protocol, please contact the study coordinator ((206-797-2704 or 206-314-9420) or transfusion service laboratory (UWMC 598-6240, HMC 744-3088, UWMC NW (Maggie Green) 206-540-0146)).

Research coordinators: Kelsey Leigh Garcia (klgarcia@seattlecca.org) and Kim Quach (kquach@uw.edu)


Adverse events and cautions:
- Risk of transfusion reactions including TRALI and blood-borne pathogen infection.
- Contraindicated in IgA deficiency or in patients with a history of transfusion reaction; caution in volume overload.
- Theoretical risk of worsening clinical course due to antibody-dependent enhancement, which has been described for MERS-CoV, or possibly through non-specific immune activation should be considered.

Administration:
1 unit IV once

Pregnancy: Pregnant and breastfeeding people are allowed under the expanded access program (Mayo clinic), NCT04348656. In a small case series of four critically ill patients in China who received convalescent plasma and recovered from COVID-19, one of the patients was pregnant.11
References


These guidelines were drafted by a working group, including Fred Buckner, Jeannie Chan, Guang-Shing Cheng Shireesha Dhanireddy, Margaret Green, Robert Harrington, Josh Hill, Rupali Jain, Christine Johnston, H. Nina Kim, David Koelle, Manoj Menon, Sylvia LaCourse, Paul Pottinger, Alpana Waghmare, Anna Wald, Anne Woolfrey, and Mark Wurfel

Additional input regarding pregnant and lactating individuals provided by Kristina Adams Waldorf, Edith Cheng, Jane Hitti, Christopher Kim, Kimberly Ma, Jennie Mao, Rena Patel, Stephen McCartney, LaVone Simmons

Additional input regarding cardiac monitoring was provided by Neal Chatterjee, Stephanie Cooper, Kevin O’Brien, Arun Sridhar