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

Evidenced-based treatment for SARS-CoV-2 infection has evolved rapidly since the novel virus was identified in January 2020. Clinical trial data is 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. These guidelines are frequently updated. On October 22, 2020, IV Remdesivir (Veklury) was granted FDA-approval for treatment of SARS-CoV-2 infection among hospitalized adults and children aged 12 and older. The UW Medicine Treatment Guidelines will address institution specific practices, including availability of clinical trials within UW Medicine.

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 Infectious Diseases Consult team with questions about inpatient management of specific patients and refer to national published guidelines for recommendations.


From the NIH COVID-19 guidelines:

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

<table>
<thead>
<tr>
<th>DISEASE SEVERITY</th>
<th>PANEL’S RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Hospitalized or Hospitalized but Does Not Require Supplemental Oxygen</td>
<td>No specific antiviral or immunomodulatory therapy recommended. The Panel recommends against the use of dexamethasone (AI). See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.</td>
</tr>
<tr>
<td>Hospitalized and Requires Supplemental Oxygen (but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)</td>
<td>Remdesivir 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first (AI)(^{\text{cd}}). or Remdesivir (dose and duration as above) plus dexamethasone* 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first (BIll)(^{\text{f}}). If remdesivir cannot be used, dexamethasone* may be used instead (BIll)</td>
</tr>
<tr>
<td>Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation</td>
<td>Dexamethasone(^{\text{g}}) plus remdesivir at the doses and durations discussed above (AIII)(^{\text{f}}) or Dexamethasone(^{\text{g}}) at the dose and duration discussed above (AI)</td>
</tr>
<tr>
<td>Hospitalized and Requires Invasive Mechanical Ventilation or ECMO</td>
<td>Dexamethasone(^{\text{g}}) at the dose and duration discussed above (AI) or Dexamethasone(^{\text{g}}) plus remdesivir for patients who have recently been intubated at the doses and durations discussed above (CIII)(^{\text{f}})</td>
</tr>
</tbody>
</table>

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

\(^{\text{a}}\) The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.

\(^{\text{b}}\) Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

\(^{\text{c}}\) The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.

\(^{\text{d}}\) For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

\(^{\text{e}}\) If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See Corticosteroids for more information.

\(^{\text{f}}\) The combination of dexamethasone and remdesivir has not been studied in clinical trials; see text for the rationale for using this combination.

Key: ECMO = extracorporeal membrane oxygenation; IV = intravenously; PO = orally
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*\(^4\).

The FDA approved IV Remdesivir based on evidence from three clinical trials\(^5\)\(^-\)\(^7\).

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 1062 people. The trial (known as the *Adaptive COVID-19 Treatment Trial*, or ACTT-1), 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.

In the final analysis, patients who received remdesivir (n =541) had a median recovery time of 10 days (95% CI, 9 to 11 days) compared to 15 days (95% CI 13-18 days) among those who received placebo (n =521) The Kaplan-Meier estimates of mortality were 11.4% with remdesivir and 15.2% with placebo by day 29 (HR, 0.73; 95% CI, 0.52 to 1.03). In the subgroup of 435 patients who required supplemental oxygen (but not high flow, non-invasive ventilation, invasive mechanical ventilation or ECMO), significantly improved time to recovery was demonstrated compared to placebo (recovery rate ratio 1.45 95% CI 1.18-1.79) In this group, remdesivir conferred a significant survival benefit (HR for death 0.30, 95% CI, 0.14 to 0.64). In patients who required high-flow oxygen or noninvasive ventilation at enrollment (n=193), there was no observed difference in time to recovery (recovery rate ratio 1.09 , 95% CI 0.76 to 1.57). Among patients who were on mechanical ventilation or ECMO at baseline (n = 285), there was no observed difference in time to recovery between remdesivir and placebo (recovery rate ratio 0.98; 95% CI 0.70-1.36).

Remdesivir was studied in a randomized, open-label of patients with moderate COVID-19 pneumonia, defined as the presence of pulmonary infiltrates but not requiring supplemental oxygen (room air O2 saturation>94%)\(^6\). Participants received remdesivir (10 day course), remdesivir (5 day course) or standard therapy. The primary outcome was based on improvement in a 7-point ordinal scale on Day 11. The odds of a favorable clinical status was increased in the remdesivir 5-day group (OR=1.65, p=0.02) but not in the 10-day group (p=0.18). Nausea, hypokalemia and headache were more frequent in the remdesivir treated patients. The IDSA guidelines recommend against the use of remdesivir in this patient population given a very low certainty of evidence\(^8\). NIH Guidance does not recommend for or against IV remdesivir in this patient population due to insufficient data, but recognizes that in certain situations, such as in patients with high-risk of clinical progression, clinicians may choose to use remdesivir among hospitalized patients with moderate COVID-19.

The SOLIDARITY trial was a World Health Organisation-sponsored open-label, randomized trial comparing different investigational interventions plus standard of care to standard of care alone in hospitalized patients.
Remdesivir was studied in one arm of the study. The SOLIDARITY trial did not find a statistically significant difference in mortality between the remdesivir arm and the standard of care arm.

Duration:

The optimal duration of IV remdesivir was evaluated in 397 patients hospitalized with COVID-19. Patients were randomized to 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. The NIH guidance recommends a five day duration for all populations but can be extended up to 10 days if no substantial clinical improvement is seen at Day 5. Of note, this differs slightly from the FDA prescribing information for remdesivir, which recommends a 10 day course of therapy for patients receiving ECMO or mechanical ventilation. The UW Medicine Guidelines are consistent with NIH guidance, which recommends starting with a 5 day course of therapy.

At UW Medicine, we will continue to use an approval mechanism for remdesivir due to the high cost of this medication and to ensure appropriate use of this medication. To request IV remdesivir for patients who meet criteria for treatment, please complete the survey by clicking on the link provided below. Providers will be asked to enter contact information, the patient’s MRN, and key clinical information into the secure form. Requests will be reviewed by the UW Medicine Pharmacy & Therapeutics Committee and decisions will be made based on the UW Medicine COVID Treatment Guidelines within 24 hours.

Link to request remdesivir:

https://redcap.link/remdesivirEUA_UW

Precautions:

- Hypersensitivity including infusion related and anaphylactic reactions. Hypersensitivity reactions have been observed during and following the administration of remdesivir (Veklury).
- Increased risk of transaminase elevation. Perform baseline hepatic laboratory testing in all patients prior to starting therapy. Consider discontinuing IV remdesivir if ALT levels increase to > 10 ULN. Discontinue therapy if ALT elevation is accompanied by signs or symptoms of liver inflammation.
- IV remdesivir is not recommended for patients with a GFR ≤ 30 ml/min due to the vehicle in (SBECO) in the intravenous formulation, but due to short course and experience with this vehicle in other FDA approved products (i.e. Voriconazole), this will not be an exclusion criteria for therapy at UW Medicine.
- Contraindicated in patients with known hypersensitivity to remdesivir
- Reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine.

Dosing:

200 mg IV x 1 on Day 1, followed by 100 mg IV daily

Duration:
• A 5 day course of remdesivir will be prescribed to all hospitalized patients. The course can be continued up to 10 days if patient does not demonstrate substantial improvement by day 5. Patients who otherwise meet criteria for discharge before day 5, patient should be discharged without continuing therapy.

• FDA prescribing information for remdesivir recommends a 10 day course of therapy for patients receiving ECMO or mechanical ventilation. The UW Medicine Guidelines are consistent with NIH guidance, which recommends starting with a 5 day course of therapy.

Suggested Monitoring:

• Daily CBC, Chemistries, and Liver enzymes
• If ALT > 10 x ULN, stop medication.
• Patient education materials can be found here: https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_patient_pi.pdf

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 remdesivir13. 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. Among 86 pregnant women who received compassionate use remdesivir for treatment of severe COVID-19, the medication was well tolerated14. Although 16% of the population experienced SAEs, most of these were due to pregnancy and underlying disease. There was one death due to underlying disease and no deaths attributed to remdesivir.

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 12 years of age with confirmed COVID-19 and severe manifestations of disease.
Dexamethasone:

Based on preliminary analysis of the data from the RECOVERY trial, both IDSA and NIH issued the following recommendations for use of corticosteroids among these patient 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 <strong>against</strong> the use of dexamethasone (A1)</td>
<td>Recommends <strong>against</strong> the use of glucocorticoids (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 <strong>up to 10 days</strong> (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>Require delivery of oxygen through a high-flow device or non-invasive ventilation or Mechanically ventilated</td>
<td>Dexamethasone recommended 6mg IV/PO daily for <strong>up to 10 days</strong> (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\textsuperscript{15}. 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)\textsuperscript{15}.

A meta-analysis of 7 randomized trials using steroids to treat COVID-19 disease among critically ill patients showed a mortality benefit to use of steroids (summary OR=0.66, 95% CI=0.53-0.82, p<0.001).\textsuperscript{16} Although dexamethasone was the only therapy that was significantly associated with decreased mortality, hydrocortisone and methylprednisolone were underpowered but showed trends toward favorable outcomes as well. When possible, dexamethasone should be used.
Considerations:

Before initiating dexamethasone, clinicians should evaluate the patient’s medical history and assess the potential and benefits including co-pathogens such as influenza\textsuperscript{17}. Patient may experience hyperglycemia, neurological side effects, adrenal suppression and may be at risk increased bacterial infections. Presence of co-infections should be evaluated. In severe viral pneumonia caused by influenza, corticosteroid therapy appears to result in worse clinical outcomes, including secondary bacterial infection and death\textsuperscript{18}.

Strongyloidiasis is caused by a nematode (roundworm) infection. \textit{Strongyloides} infection is predominantly acquired through contact with soil contaminated with free-living larvae, which penetrate the skin and migrate to the intestine, where they lay eggs. Although a majority of individuals with strongyloidiasis are asymptomatic, a severe disease manifestation is hyperinfection syndrome. The most common precipitator severe disease is use of a corticosteroid agent, which appears to be independent of dose or duration of treatment. Based on the available data, the benefit of dexamethasone outweighs the risk of possible \textit{Strongyloides} hyperinfection, an uncommon complication. However, due to the high mortality associated with this syndrome and the availability of inexpensive and effective therapy, ivermectin could be used as a preventive strategy for at-risk patients. \textbf{No serology or laboratory confirmation is needed prior to treatment}\textsuperscript{19}.

\begin{itemize}
  \item \textbf{A.} Birth or residence or long-term travel (> 6 months) in\textsuperscript{20}:
    \begin{itemize}
      \item Southeast Asia, Oceania, Sub-Saharan Africa, South America, Caribbean: Treat with ivermectin
      \item Mediterranean countries, Middle East, North Africa, Indian sub-continent, Asia: Treat with ivermectin only if exposure to rural or beach areas with skin contact to soil or sand. Otherwise, the risk is low and do not treat with ivermectin.
      \item Australia, North America (including Mexico) or Western Europe: low-risk, do not pre-emptively treat
    \end{itemize}
  \item \textbf{B.} Treatment: Ivermectin 200 $\mu$g/kg/day (round to the nearest 3mg tablet) po once daily x 2 doses on day 1 and 2
\end{itemize}

Corticosteroids may increase the risk of reactivation of latent infections (such as hepatitis B, herpes viruses, strongyloides or tuberculosis). PJP prophylaxis is not needed for short-term treatment with dexamethasone\textsuperscript{21}. If patients are on additional immunosuppression, PJP prophylaxis may be considered.

It is not known whether other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, will have a similar benefit to dexamethasone. Of note, the dose equivalents for dexamethasone 6 mg daily are prednisone 40 mg, methylprednisolone 32 mg, and hydrocortisone 160 mg.

Duration:

The duration of the dexamethasone was 6mg IV/PO for up to 10 days. If patients are otherwise ready for discharge before they have completed the 10 day course, dexamethasone may be discontinued. 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.

Clinical Trials Available at UW Medicine

Outpatient Studies

For available clinical trials, visit the ITHS website: https://www.iths.org/iths-covid-19-research-resources/current-covid-19-research/
SARS CoV-2 Convalescent Plasma

On August 23, 2020, FDA issued an EUA for COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The NIH Guidelines do not recommend for or against CP for treatment of COVID-19, citing a lack of evidence. The IDSA Guidelines recommend COVID-19 convalescent plasma only in the context of a clinical trial. When available, patients should be offered enrollment into randomized controlled trials. At this time, there is an ongoing randomized clinical trial at UW Medicine (PassItOn). If desired, CP is available at UW Medicine through transfusion services. CP can be ordered using the COVID-19 Convalescent Plasma orderset in ORCA.

Mechanism of Action:

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

Evidence Summary:

Convalescent plasma (CP) has been administered since the late 19th century for a variety of infectious and non-infectious entities, most notably influenza (1918, 2009 H1N1 and 2007 H5N1), SARS CoV-1, SARS CoV-2 infections. An exploratory meta-analysis of these earlier 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 includes case series with or without propensity-matched “control” patients, and a few small RCTs. The RCT have not included non-convalescent control plasma. 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). However, the study was stopped early due to inability to recruit cases and therefore was underpowered to detect a significant difference.

A 1:1 randomized RCT of CP plus standard of care of hospitalized COVID-19 patients found no differences in 60-day mortality, length of stay, or day 15 severity. While patients were treated early (median 10 days of symptoms), most had endogenous antibody when treated. Donor CP with the highest available neutralizing titer was used. In small subgroups, the increase in patient antibody levels at day 7 after treatment was similar between CP-treated and control patients. The study was stopped early by the DSMB due to the presence of endogenous antibody in most recipients and lack of efficacy during interim analysis.

Recently Joyner et al. reported outcome data on 35,322 US recipients treated with CP during April, May, and June 2020. Inclusion criteria were liberal for patients with or at risk for severe COVID-19. Analyses were clustered by duration of symptoms prior to receipt, calendar interval reflecting evolving standards of care, and level of CP anti-SARS-CoV-2 antibody by ELISA, available on ~9% of the CP units. Overall, 27% of patients were ventilated at time of CP. During the 3 month study, CP recipients trended to less ill and a shorter duration of illness prior to CP receipt. The primary endpoints were 7 and 30 day crude mortality. There were no propensity-matched controls. Mortality rates were lower for persons treated within 3 days of symptoms vs. later in each of the 3 months, for persons in each age strata, and for persons on or off the ventilator at time of treatment.
Mortality rates were lower in persons treated with high titer CP. Combined analyses of days of symptoms and CP titer showed that early and high titer treatment were each associated with lower mortality. For example, adjusted 30 day mortality was 30% in persons treated at 4 or more days of illness with lower titer CP, versus 20% in persons treated within 3 days with high titer CP. Subgroup analyses of CP titer vs. outcome in patient groups varying by ventilator status, severe risk factors, and time of treatment generally did not, however, reach significance.

**Adverse events and cautions:**

- CP appears to be safe in a review of 20,000 doses\(^{34}\). Mortality occurred in 63 (0.3%) of persons within 4 hours of CP. Of these, 13 were considered possibly or probably related to CPI.
  - Risk of transfusion reactions including TRALI, TACO, severe allergic reactions, 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: 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\(^{35}\). 
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