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.


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

<table>
<thead>
<tr>
<th>Table 1. Treatment options based on patient population with COVID-19</th>
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<tbody>
<tr>
<td><strong>Outpatient</strong></td>
</tr>
<tr>
<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>COVID-19 positive hospitalized patient without radiographic evidence of COVID-19 pneumonia and not requiring supplemental oxygen</strong></td>
</tr>
<tr>
<td>Recommend against use of Remdesivir use link to request <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a> 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>
</tr>
<tr>
<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.</td>
</tr>
<tr>
<td>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” The NIH and IDSA Guidelines do not recommend for or against Convalescent Plasma. If desired, convalescent plasma (CP) is available thru transfusion services: use COVID-19 Convalescent Plasma orderset in ORCA. To order at Northwest, use transfusion medicine orderset in Soarian.</td>
</tr>
<tr>
<td><strong>LRTI with mechanical ventilation</strong></td>
</tr>
<tr>
<td>Recommend Dexamethasone 6mg daily for up to 10 days; discontinue at discharge.</td>
</tr>
<tr>
<td>Consider IV Remdesivir; Use link to request: <a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a> The NIH and IDSA Guidelines do not recommend for or against Convalescent Plasma. If desired, convalescent plasma (CP) is available thru transfusion services: use COVID-19 Convalescent Plasma orderset in ORCA. To order at Northwest, use transfusion medicine orderset in Soarian.</td>
</tr>
<tr>
<td><strong>Pregnant patients with LRTI</strong></td>
</tr>
<tr>
<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>
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-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-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.

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 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.

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%)\(^7\). 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.

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 in hospitalized adult and pediatric patients with COVID-19\(^8\)\(^-\)\(^9\). This drug is not FDA approved but will be available on a limited basis at
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.

**Table 2. Available Mechanisms to Obtain Remdesivir at UW Medicine**

<table>
<thead>
<tr>
<th>Emergency Use Authorization</th>
<th>Target population</th>
<th>Precautions</th>
<th>Informed Consent</th>
<th>Availability and Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized patients (including pregnant women) with confirmed SARS-CoV-2 by PCR AND severe disease defined as patients with oxygen saturation (SpO2) &lt; 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 formal informed consent. Provide “FDA Fact Sheet” to patient or family members  See below for additional documentation needed</td>
<td>HMC, UWMC-ML, UWMC-NW and Valley (<a href="https://redcap.link/remdesivirEUA_UW">https://redcap.link/remdesivirEUA_UW</a>)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Inclusion Criteria</th>
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</tr>
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<tbody>
<tr>
<td>Hospitalized children &lt;18 yo with confirmed CoVID-19 and severe manifestation of disease</td>
<td>1) Evidence of multi-organ failure 2) Use of more than 1 pressor to maintain blood pressure 3) ALT levels &gt; 5x ULN 4) GFR &lt;30 mL/min or dialysis or continuous veno-venous hemofiltration 5) Use of other experimental antiviral agents for COVID-19.</td>
</tr>
</tbody>
</table>

**Emergency Authorization Use**

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);
- 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.

**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](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 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.

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>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. 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).
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{12} 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{13}. 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{14}.

Strongyloidiasis is caused by a nematode (roundworm) infection. *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 *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. No serology or laboratory confirmation is needed prior to treatment\textsuperscript{15}.

A. Birth or residence or long-term travel in\textsuperscript{16}:
   a. Southeast Asia, Oceania, Sub-Saharan Africa, South America, Caribbean: Yes
   b. Mediterranean countries, Middle East, North Africa, Indian sub-continent, Asia: Optional
   c. Australia, North America (including Mexico) or Western Europe: low-risk, do not pre-emptively treat

B. Treatment: Ivermectin 200 µg/kg/day (round to the nearest 3mg tablet) po once daily x 2 doses on day 1 and 2

Corticosteroids may increase the risk of reactivation of latent infections (such as hepatitis B, herpesvirues, strongyloides or tuberculosis). PJP prophylaxis is not needed for short-term treatment with dexamethasone\textsuperscript{17}. 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 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 corticosteroids and remdesivir are not known.

**Duration of therapy:**

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.

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.idssociety.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. 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.

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

For available clinical trials, visit the ITHS website: [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/)
**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 are no RCT of CP available at UW Medicine.

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, and MERS CoV 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\(^{30}\). 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\(^{31}\).
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