

# Denver Health Treatment Guidance for SARS-CoV-2 Infection/COVID-19

## GENERAL PRINCIPLES

- As the optimal treatment of COVID-19 is unknown, patients should be enrolled in DH clinical trials whenever possible.
- If patients are not eligible for clinical trials or decline to participate, investigational therapies may be considered on a case by case basis after discussion of risks and benefits with the patient/family.
- Patients and families should understand that it is not known whether any given investigational therapy will provide benefit and it may have the potential to cause harm.
- Risk factors for progression to severe disease include: age  $\geq 65$  years, chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic liver disease, immunosuppressing medication or condition, severe obesity (BMI  $\geq 40$ )
- Treatment guidance is likely to evolve. Refer to the COVID subsite or DH Antibiotic App for the most up to date guidance.
- This is intended only as a guide for evidence-based decision-making; it is not intended to replace clinical judgment.

Clinical Scenario	Treatment
Outpatients and hospitalized adults not requiring oxygen	Supportive care
Hospitalized adult with hypoxemia, requiring supplemental oxygen or mechanical ventilation	<ul style="list-style-type: none"> <li>• Supportive care</li> <li>• Dexamethasone* 6 mg IV/PO once daily x 10 days or until hospital discharge, whichever comes first</li> <li>• Consider clinical trial enrollment for therapeutic agents (see trials below)               <ul style="list-style-type: none"> <li>• If not eligible or declines to participate in trials:                   <ul style="list-style-type: none"> <li>○ Consider remdesivir under emergency use authorization (EUA) (see criteria for use below). Use of remdesivir under EUA is not an exclusion criterion for most studies – refer to specific study criteria below.</li> <li>○ Consider addition of convalescent plasma (see criteria for use below)</li> </ul> </li> </ul> </li> </ul>
Hospitalized pediatric patient	<ul style="list-style-type: none"> <li>• Supportive care</li> <li>• Consider remdesivir under emergency use authorization (Consult Pediatric ID Attending)</li> <li>• Consider dexamethasone (on a case-by-case basis with discussion between PICU and ID)</li> </ul>
Exposure to a patient or close contact known to be SARS-CoV-2 positive	Post-exposure prophylaxis is not recommended
*Alternative corticosteroids can be used if dexamethasone is unavailable. Equivalent doses: prednisone 40 mg daily, methylprednisolone 32 mg daily, hydrocortisone 160 mg daily – WHO recommends 50 mg IV Q8H if hydrocortisone is used.	

## DENVER HEALTH CLINICAL TRIALS (Active)

### **ACTT3 - Remdesivir +/- Rebif (Interferon beta-1a) (ACTIVE)**

- PI: Dave Wyles; Coordinator: Amy Irwin
- Phase 3 RCT - All patients will receive remdesivir for up to 10 days, and Rebif (Interferon beta-1a) or a Placebo, every other day, for a total of 4 doses.
- Inclusion (select):

- Admitted to a hospital with symptoms suggestive of COVID-19.
- Male or non-pregnant female adult  $\geq 18$  years of age at time of enrollment.
- Laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health in any respiratory specimen, as documented by either of the following:
  - PCR or other assay positive in sample collected  $< 72$  hours prior to randomization; OR
  - PCR or other assay positive in sample collected  $\geq 72$  hours but  $< 7$  days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
- Illness of any duration, and at least one of the following:
  - Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR
  - SpO<sub>2</sub>  $\leq 94\%$  on room air, OR
  - Requiring supplemental oxygen, OR
- Agrees to not participate in another clinical trial (both pharmacologic and other types of interventions) for the treatment of COVID-19 through Day 29.
- Exclusion (select):
  - Anticipated discharged from the hospital or transfer to another hospital within 72 hours.
  - High flow O<sub>2</sub> or ventilation
  - ECMO
  - eGFR  $< 30$  mL/min, unless in the opinion of the PI, the potential benefit of receiving remdesivir outweighs the potential risk of study participation.
  - ALT or AST  $> 5$  times the upper limit of normal.
  - WBC  $< 1500$  cells/ $\mu$ L or platelet count  $< 50,000/\mu$ L.
  - History of chronic liver disease (e.g., jaundice, ascites, hepatic encephalopathy, history of bleeding esophageal or gastric varices). No laboratory testing is needed.
  - Pregnancy
  - Received three or more doses of remdesivir, including the loading dose, outside of the study for COVID-19.
  - Received convalescent plasma or intravenous immunoglobulin [IVIG] for the treatment of COVID-19.
  - Received any interferon product within two weeks of screening, either for the treatment of COVID-19 or for a chronic medical condition (e.g., multiple sclerosis, HCV infection).
  - Received any of the following in the two weeks prior to screening as treatment of COVID-19:
    - small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatinib, gefitinib, acalabrutinib, etc.);
    - monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab], etc.);
    - monoclonal antibodies targeting T-cells or B-cells as treatment for COVID-19

### ACTIV3 - Remdesivir +/- monoclonal antibody (ACTIVE)

- PI: Ed Gardner; Coordinator: James Scott
- Phase 3 RCT – All patients will receive remdesivir for up to 10 days + either a monoclonal antibody targeting SARS-CoV2 spike protein or placebo.
- Inclusion criteria (select)
  - Age  $\geq 18$  years;
  - Informed consent by the patient or the patient's legally-authorized representative (LAR)
  - SARS-CoV-2 infection, documented by PCR or other nucleic acid test (NAT) within 3 days prior to randomization OR documented by NAT more than 3 days prior to randomization AND progressive disease suggestive of ongoing SARS-CoV-2 infection;
  - Duration of symptoms attributable to COVID-19  $\leq 12$  days;
  - Requiring admission for inpatient hospital acute medical care for clinical manifestations of COVID-19
  - *Patients already on remdesivir/steroids can still enroll in this study*
- Exclusion criteria (select)
  - Prior receipt of any SARS-CoV-2 IVIG or convalescent plasma
  - Not willing to abstain from participation in other COVID-19 treatment trials until after day 5;
  - Expected inability to participate in study procedures;
  - Women of child-bearing potential who are not already pregnant at study entry and who are unwilling to decrease pregnancy risk.
  - Men who are unwilling to abstain from sexual intercourse or use barrier contraception with women of child-bearing potential.
  - [Phase 2 portion only] Presence at enrollment of any of the following:
    - a. stroke
    - b. meningitis
    - c. encephalitis
    - d. myelitis
    - e. myocardial infarction

- f. myocarditis
- g. pericarditis
- h. symptomatic congestive heart failure (NYHA class III-IV)
- i. arterial or deep venous thrombosis or pulmonary embolism
- [Phase 2 portion only] Current or imminent requirement for any of the following:
  - a. invasive mechanical ventilation
  - b. ECMO
  - c. mechanical circulatory support
  - d. vasopressor therapy
  - e. commencement of new renal replacement therapy at this admission

#### **COVASTIL - Anti-ST2/IL-33)/Placebo vs. UTTR1147A (IL-22Fc)/Placebo (ACTIVE)**

- PI: Dr. Douglas; Coordinator: Terra Hiller
- Phase 2 RCT – will receive one dose of either compound, optional second dose if the patient is hospitalized requiring O2 on Day 15
- Inclusions:
  - Age ≥18 years
  - Hospitalized with COVID-19 pneumonia confirmed and evidenced by chest X-ray or CT scan
  - Peripheral capillary oxygen saturation (SpO2) ≤93% or partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) ≤300 mmHg or requiring supplemental oxygen to maintain SpO2 ≤ 93%
- Exclusions:
  - Pregnant or breastfeeding, or intending to become pregnant during the study or within 95 days after the final dose of study drug
    - Women of childbearing potential must have a negative serum pregnancy test result within 7 days prior to initiation of study drug.
  - Participating in another clinical drug trial
  - Treatment with investigational therapy (other than for COVID-19) within 5 half-lives or 30 days (whichever is longer) prior to initiation of study drug
  - Use of Janus kinase (JAK) inhibitor within 30 days or 5 drug elimination half-lives (whichever is longer) prior to screening
  - Have received high-dose systemic corticosteroids (≥ 1 mg/kg methylprednisolone or equivalent) within 72 hours prior to Day 1
  - Known HIV infection with CD4 < 200 cells/μL or < 14% of all lymphocytes
  - ALT or AST > 10 x upper limit of normal (ULN) detected at screening
  - History of cancer within the previous 5 years unless it has been adequately treated and considered cured or remission-free in the investigator's judgment
  - Clinical evidence of active or unstable cardiovascular disease (e.g., acute myocardial ischemia or decompensated heart failure) as assessed by the investigator

#### **tpA (salvage/compassionate use) – BARDA (ACTIVE)**

- PI: Gene Moore, MD; Coordinator: Arsen Ghasabyan 303.602.3795, Caitlin Robinson 303.602.1863
- Phase 2a, open label trial with modified stepped-wedge design
- Inclusion: Patients with known or suspected COVID-19 infection with a PaO2/FiO2 ratio < 150 (at sea level) or inferred PaO2/FiO2 ratio from SpO2 if ABG is unavailable persisting for > 4 hours despite maximal mechanical ventilation management according to each institution's ventilation protocols. Patients will be enrolled based on clinical features, without consideration of language (using hospital interpreters and translated consent), race/ethnicity, or gender
- Exclusion (not all inclusive list):
  - Exclusions for receiving tpa ie active bleeding, uncontrolled HTN, platelets <100 x 10<sup>9</sup>/L, etc
  - Hemodynamic instability
  - Acute Renal failure (escalating renal failure with creatinine >3 times baseline)
  - Liver failure (escalating liver failure with ALT > 3 times baseline)
  - Is currently on ECMO

#### **INVESTIGATIONAL THERAPIES (use outside of clinical trials)**

##### **Remdesivir**

Data from two published randomized, controlled trials support the use of remdesivir for hospitalized patients with severe COVID-19. Given this and that there is no other approved therapy, the FDA granted emergency use authorization (EUA). The federal government is providing state health departments with allocations for states to distribute to hospitals/systems. This supply was initially donated, now hospitals must purchase or decline their allotment. Due to the

limited supply and cost, a pharmacist must place the order. ID Consult is not required, but could be consulted for questions.

Suggested criteria for use at Denver Health:

1. Hospitalized with laboratory-confirmed COVID-19
2. Requiring supplemental oxygen to maintain oxygen saturation  $\geq 90\%$  OR mechanical ventilation
3. Expected hospital stay of at least 3 days from the start of treatment
4. Not already clinically improving
5. Patient or caregiver verbally consents to treatment after discussion of investigational nature of therapy and potential risks/benefits/alternatives. If patient or caregiver are unable to provide verbal consent, the provider may prescribe remdesivir if the potential benefit outweighs potential risk.
6. ID Consult is not required, but may be consulted if questions

Relative or absolute contraindications:

1. CrCl < 30 mL/min (relative contraindication)
2. ALT/AST > 5x ULN (absolute contraindication)

See FDA Provider Fact Sheet for contraindications/monitoring parameters/etc:

<https://www.fda.gov/media/137566/download>

See FDA Patient Fact Sheet for risk/benefit discussion:

English <https://www.fda.gov/media/137565/download>

Spanish [https://www.remdesivir.com/us/downloads/Fact\\_Sheet\\_for\\_Patients\\_and\\_Caregivers\\_Spanish.pdf](https://www.remdesivir.com/us/downloads/Fact_Sheet_for_Patients_and_Caregivers_Spanish.pdf)

Recommended dose: 200 mg IV x 1 dose, then 100 mg IV Q24H x 4 doses. In selected cases, treatment course may be extended to 10 days.

Monitoring: Patients should have baseline renal function determined. Patients should also have hepatic laboratory testing performed prior to initiation and daily while receiving remdesivir.

References:

1. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of COVID-19 – preliminary report. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2007764
2. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 of 10 days in patients with severe Covid-19. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2015301

### **Dexamethasone**

Data from randomized controlled trials and a meta-analysis by the WHO demonstrated a reduction in mortality with use of corticosteroids for patients who require supplemental oxygen or mechanical ventilation. Use of corticosteroids may *increase* mortality when used in patients who do not require supplemental oxygen and should not be used in this scenario.

Reference:

1. RECOVERY trial. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N Eng J Med* 2020. DOI: 10.1056/NEJMoa2021436
2. CoDEX trial. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19. *JAMA* 2020. doi:10.1001/jama.2020.17021
3. WHO REACT Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19 A Meta-analysis. *JAMA* 2020. doi:10.1001/jama.2020.17023.

### **Convalescent Plasma**

On August 23, 2020, the FDA issued an emergency use authorization (EUA) for COVID-19 convalescent plasma (CCP) for the treatment of COVID-19 in hospitalized patients. Based on the scientific evidence available, the FDA concluded this product may be effective in treating COVID-19 and that the known and potential benefits of the product outweigh the known and potential risks of the product.

Suggested criteria for use at Denver Health:

- 1) Hospitalized with laboratory-confirmed COVID-19
- 2) Requiring  $\geq 4$ L oxygen to maintain oxygen saturation  $\geq 90\%$  OR mechanical ventilation
- 3) One or more risk factor for progression to severe disease: age  $\geq 65$  years, chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic liver disease, immunosuppressing medication or condition, severe obesity (BMI  $\geq 40$ ) (in severe disease, CCP may be considered in the absence of any risk factors)
- 4) Not already clinically improving
- 5) Patient or LAR/proxy consents to treatment after discussion of investigational nature of therapy and potential risks/benefits/alternatives

**Note:** CCP may be considered in other clinical scenarios based on provider judgment

Relative or absolute contraindications:

- 1) History of transfusion reaction (e.g., severe allergic reaction or anaphylaxis to blood products)
- 2) Pregnancy
- 3) Co-existing condition in which clinicians determine the risk of transfusion exceeds potential benefit (e.g., due to hyperosmolality of plasma)
- 4) Critical illness such that imminent death is expected

See FDA Provider Fact Sheet for risk/benefit discussion: <https://www.fda.gov/media/141478/download>

Recommended dose: Transfuse 1 unit ( $\approx 200$ mL) of CCP. Transfusion of an additional 1 unit may be considered based on clinical response and provider judgment.

Monitoring:

- Monitor for evidence of transfusion reactions including TRALI and TACO

Steps to administer convalescent plasma:

1. Call Infectious Diseases attending to discuss case if considering use of convalescent plasma
2. If patient is enrolled in a clinical trial, determine whether convalescent plasma administration is allowed and discuss with trial PI before proceeding
3. Discuss the investigational nature and potential risks, benefits, and alternatives to CCP with the patient or LAR/proxy and provide the FDA Patient Fact Sheet: English <https://www.fda.gov/media/141479/download> Spanish <https://www.fda.gov/media/141984/download>
4. If the patient or LAR/proxy consents to treatment, enter a Treatment Plan note. The dot phrase “convalescent plasma” may be used: “This patient has severe COVID-19 and we have elected to treat with COVID-19 convalescent plasma (CCP) under the FDA Emergency Use Authorization (EUA). In accordance with the EUA, we have discussed the following with the patient or LAR/proxy: 1) potential risks and benefits of CCP, 2) the alternatives to CCP, and 3) that CCP has not been approved or licensed by the FDA but is authorized for use under the EUA. The patient or LAR/proxy has been provided with the FDA-approved fact sheet and has consented to this treatment.”
5. “Informed Consent for Transfusion of Blood and Blood Products” form completed by primary team
6. After consent obtained, place Epic order for “Type and Screen” and “Prepare& Transfuse FFP” found in the Adult Blood Product Administration order set. **In the FFP order comment, enter “COVID convalescent plasma.”**
7. Serious adverse events or deaths potentially attributable to the transfusion must be reported to the FDA using the MedWatch FDA Form 3500 available at: <https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting>

References:

1. Chen L, et al. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis* 2020: [https://doi.org/10.1016/S1473-3099\(20\)30141-9](https://doi.org/10.1016/S1473-3099(20)30141-9).
2. Duan K, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv preprint doi: <https://doi.org/10.1101/2020.03.16.20036145>.
3. Mair-Jenkins J, et al. The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis. *The Journal of Infectious Diseases* 2015;211:80–90
4. Shen C, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020. doi:10.1001/jama.2020.4783
5. Zhan B, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *CHEST* 2020, doi: <https://doi.org/10.1016/j.chest.2020.03.039>.

6. Joyner M, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients medRxiv preprint doi: <https://doi.org/10.1101/2020.05.12.20099879>. Posted May 14, 2020.
7. Liu S, et al. Convalescent plasma treatment of severe COVID-19: A matched 1 control study. medRxiv preprint doi: <https://doi.org/10.1101/2020.05.20.20102236>. Posted May 22, 2020
8. Joyner M, et al. Evidence favoring the efficacy of convalescent plasma for COVID-19 therapy. medRxiv preprint July 30, 2020. doi: <https://doi.org/10.1101/2020.07.29.20162917>
9. Joyner M, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv preprint Aug 12, 2020. doi: <https://doi.org/10.1101/2020.08.12.20169359>
10. U.S. Food & Drug Administration News Release. Available at <https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment> (accessed 8/26/20)

### Hydroxychloroquine

Although early in vitro data and observational data suggested a potential benefit of hydroxychloroquine, randomized trials have yielded unfavorable results and there have been an increasing number of reports suggesting the potential for harm may outweigh the potential benefit. With an increase in evidence suggesting no benefit to harm with HCQ, the FDA removed its EUA. For this reason, hydroxychloroquine should not be used.

#### References:

1. Yao X, Ye F, Zhang M, et al. *In Vitro* Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. 2020; pii: ciaa237.
2. Wang M, Cao R, Zhang L, et al. Remdesivir and Chloroquine Effectively Inhibit the Recently Emerged Novel Coronavirus (2019-nCoV) *In Vitro*. *Cell Res*. 2020; 30(3): 269-271.
3. Colson P, Rolain JM, Lagier JC, et al. Chloroquine and Hydroxychloroquine as Available Weapons to Fight COVID-19. *Int J Antimicrob Agents*. 2020: 105932. [Epub ahead of print].
4. Xu X, et al. Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv:202003.00026v1
5. Chen Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. <https://doi.org/10.1101/2020.03.22.20040758>
6. Tang W, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv April 2020. <https://doi.org/10.1101/2020.04.10.20060558>.
7. Magagnoli J, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv. April 2020. <https://doi.org/10.1101/2020.04.16.20065920>
8. Arshad S, et al. Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19. *International Journal of Infectious Diseases* 2020. <https://doi.org/10.1016/j.ijid.2020.06.099>.
9. Boulware DR, et al. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. *N Eng J Med* 2020. DOI: 10.1056/NEJMoa2016638.
10. Mehra MR, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020. [https://doi.org/10.1016/S0140-6736\(20\)31180-6](https://doi.org/10.1016/S0140-6736(20)31180-6)

### Tocilizumab (IL-6 Blockade)

Preliminary data from the COVACTA randomized controlled trial found that tocilizumab did not meet its primary endpoint of improved clinical status in patients with COVID-19 associated pneumonia, or the key secondary endpoint of reduced patient mortality. Tocilizumab should not be considered for use in patients with COVID-19.

#### CONSIDERATIONS FOR CERTAIN CONCOMITANT MEDICATIONS IN COVID-19 PATIENTS

Medication	Action
ACE-I or ARBs	<ul style="list-style-type: none"> <li>• Continue or start only in patients meeting an indication for use (e.g. cardiovascular disease)</li> <li>• DO NOT START solely and specifically for the treatment of COVID-19</li> </ul>
Statins	<ul style="list-style-type: none"> <li>• Continue or start only in patients meeting an indication for use (e.g. prevention of cardiovascular disease)</li> <li>• DO NOT START solely and specifically for the treatment of COVID-19</li> </ul>
NSAIDS	<ul style="list-style-type: none"> <li>• Continue or start only in patients meeting an indication for use (e.g. co-morbid condition)</li> <li>• NO DIFFERENCE between acetaminophen or NSAIDS as</li> </ul>

	antipyretic strategies between patients with or without COVID-19
Vitamins/Supplements (e.g. vitamin C, zinc)	<ul style="list-style-type: none"> <li>No supporting evidence is available to recommend initiating vitamins or supplements in COVID-19 patients unless otherwise indicated (e.g. scurvy, zinc deficiency, poor nutritional status, etc.)</li> </ul>

\*For rationale regarding the above recommendations on these concomitant medications, please, refer to the NIH COVID-19 2020 guidelines: <https://www.covid19treatmentguidelines.nih.gov/introduction/>

#### References:

- Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32208485>.
- American College of Cardiology. HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. 2020. Available at: <https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19>.
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