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

GENERAL PRINCIPLES

- **As there are no proven effective therapies for COVID-19, 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.
- Remdesivir under Emergency Use Authorization (EUA) may be available for select cases.
- Risk factors for progression to severe disease include: age ≥65 years, chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic liver disease, immunosuppressing medication or condition, severe obesity (BMI ≥40)
- Treatment guidance is likely to evolve rapidly. Refer to the COVID subsite or DH Antibiotic App for the most up to date guidance.

Clinical Scenario	Treatment
Outpatients	Supportive care
Hospitalized adult patient not requiring ICU-level care	Supportive care Consider clinical trial enrollment for therapeutic agents (see trials below)
Hospitalized adult patient requiring ICU-level care	Supportive care Consider clinical trial enrollment for therapeutic agents (see trials below)
Hospitalized pediatric patient	Supportive care
Exposure to a patient or close contact known to be SARS-CoV-2 positive	Post-exposure prophylaxis is not recommended

DENVER HEALTH CLINICAL TRIALS (Active or Pending)

ACTT-2 (Remdesivir + baricitinib vs remdesivir vs baricitinib vs placebo) – NIH – (ACTIVE)

- PI: Gaby Frank, MD; Coordinator: Amy Irwin 303.436.4843
- Phase 3 RCT
- Inclusion:
  - ≥ 18 yo
  - Hospitalized with confirmed SARS-CoV-2 (randomization must occur w/in 72 hrs of sample collection)
  - Illness of any duration and at least one of the following: Infiltrates on imaging, SpO2 ≤ 94, requiring supplemental O2, requiring mechanical ventilation, or ECMO
- Exclusion:
  - Participation in another clinical trial for COVID-19
  - Anticipated discharge within 72 hrs
  - ALT or AST > 5 times ULN
  - eGFR < 30 mL/min or hemodialysis

- Suspected serious, active infection other than COVID-19
- Hx of VTE within 12 weeks prior to randomization or hx of recurrent VTE
- Receipt of convalescent plasma or IVIG for COVID-19 at any time during this illness
- Receipt of cytotoxic or biologic treatments such as tocilizumab, sarilumab, rituximab, baricitinib, interferon etc within 4 wks prior to enrollment
- Has received or is receiving corticosteroids at high doses (> 10 mg per day or pred or equivalent) within 2 weeks of study entry

Convalescent Plasma for the Treatment of Patients with COVID-19 – UCH (ACTIVE)

- Expanded Access Protocol: Convalescent Plasma for the Treatment of Patients with COVID-19, AND
- A Prospective Observational Cohort Trial of outcomes and antibody responses following treatment with High-Titer Anti-SARS-CoV-2 in hospitalized COVID-19 patients
- PI: Tim Jenkins: cell 303-949-9239; Coordinators: Ruth Magtanong and Terra Hiller 303.602.1438
- Inclusion criteria:
  - 18 years of age or older (if less than 18 yo, contact FDA for emergency IND authorization)
  - Lab confirmed SARS-CoV-2
  - Moderate to severe COVID-19 defined as dyspnea, RR ≥25/min, O2 sat ≤96%, with or without abnormal radiographic pulmonary imaging
- Exclusion criteria:
  - History of transfusion reaction or contraindication to receiving plasma
  - Risk of transfusion exceeds potential benefit based on clinician or blood bank determination
  - No restrictions for use of other investigational therapies

See additional suggested Denver Health criteria, monitoring, and follow-up below.

ORCHID (hydroxychloroquine vs. placebo for inpatients) – PETAL network (ACTIVE)

- PI: Ivor Douglas, MD; Coordinator: Terra Hiller 303.602.1438
- RCT, multicenter, blinded, placebo controlled
- Inclusion:
  - Age ≥18 years
  - Currently hospitalized or in an emergency department with anticipated hospitalization.
  - Symptoms of acute respiratory infection, defined as one or more of the following:
    - Cough, fever (> 37.5° C / 99.5° F), shortness of breath, sore throat
  - Laboratory-confirmed SARS-CoV-2 infection within the past 10 days or SARS-CoV-2 laboratory test result pending plus a high clinical suspicion for COVID-19 as indicated by fulfilling all of the following:
    - Cough with duration ≤10 days
    - Bilateral pulmonary infiltrates on chest imaging (radiograph, computed tomography or ultrasound) or new hypoxemia defined as SpO2 ≤94% on room air
    - No alternative explanation for symptoms of acute respiratory infection
- Exclusion (not complete list):
  - Unable to randomize within 10 days after onset of acute respiratory infection symptoms
  - Unable to be randomized within 48 hours after hospital arrival
  - QTc >500 ms within 72 hours prior to enrollment
  - Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment

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 10^9/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 will allocations for states to distribute to hospitals/systems. Do to the limited supply, use of remdesivir under EUA requires ID approval.

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

Hydroxychloroquine

Although early in vitro data and observational data suggested a potential benefit of hydroxychloroquine, small randomized trials have yielded mixed results and there have been an increasing number of reports suggesting the potential for harm may outweigh the potential benefit. For this reason, HCQ outside of the ongoing randomized trial at Denver Health is not recommended.

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.

Convalescent Plasma

Use of convalescent plasma has been studied and shown promise in outbreaks of other severe viral respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. Although several recent case series have suggested convalescent plasma may be a promising treatment for severe COVID-19, it is important that clinicians, patients, and family members recognize its safety and effectiveness for COVID-19 are not known at this time and that this is an experimental therapy. Use of convalescent plasma may be considered for patients who are not eligible for or willing to participate in a randomized trial, who are enrolled in a trial but have a progressively worsening course (must first be discussed with trial PI), or who specifically request it as a therapy. The following information is intended to serve as a resource when convalescent plasma is considered.

Suggested criteria for consideration of convalescent plasma:

1) Laboratory-confirmed COVID-19
2) Oxygen requirement ≥5L nasal cannula or rapidly progressive hypoxemia, pneumonia, or ARDS
3) One or more risk factor for progression to severe disease: age ≥65 years, chronic lung disease, cardiovascular disease, diabetes mellitus, chronic kidney disease, chronic liver disease, immunosuppressing medication or condition, severe obesity (BMI ≥40)
4) Stable or deteriorating clinical status (not already improving clinically)
5) Less than 14 days from symptom onset preferred (not required)
6) Reasonable expectation for survival over next 7 days with supportive care (based on clinical status and comorbidities)
7) Subject or proxy is willing to provide informed consent

There is currently an adequate supply of convalescent plasma in Colorado. The Colorado Convalescent Plasma Consortium recommends administration within 3 days of hospitalization when possible to maximize efficacy. A recent observational study found a mortality benefit when given prior to intubation (Liu S, et al).

Relative or absolute contraindications (note: plasma is hyperosmolar and can cause circulatory overload)

1) Contraindication to transfusion (severe volume overload, history of anaphylaxis to blood products).
2) Severe multi-organ failure or hemodynamic instability such that imminent death is expected
3) Pregnancy
4) Known or suspected venous thromboembolism (use with caution)
5) Uncontrolled co-existing infection
6) Severe DIC needing factor replacement, FFP, cryoprecipitate
7) Active intracranial bleeding
8) Clinically significant myocardial ischemia

Administration: If patient <90kg, administer 1 unit (200mL) of convalescent plasma
If Patient >90kg, administer 2 units

Monitoring and follow-up:

- Monitor for evidence of transfusion-related lung injury (TRALI) and transfusion-associated circulatory overload (TACO) (worsening oxygenation or infiltrates)
- 4 hours post-transfusion obtain:
    - Ionized calcium
    - Coagulation assessment: INR, PTT, fibrinogen, D-dimer, CBC, TEG
- Bilateral lower extremity ultrasound 1 and 3 days after administration

Steps if considering convalescent plasma:

1. Consult Infectious Diseases COVID-19 attending to discuss case
2. If patient is enrolled in a clinical trial, determine whether convalescent plasma administration is allowed and discuss with trial PI before proceeding
3. Order a Type and Screen sample to determine compatibility with available units. Place Epic order for "Prepare FFP," found in the Adult Blood Product Administration order set. In this order, specify if 1 or 2 units based on weight as above.
4. Fill out the "Request for Convalescent Plasma" form and e-mail it to the Blood Bank at DL_LabBloodBank@dhha.org.
5. Obtain informed consent for the Expanded Access Protocol, Observational Study, and Denver Health Blood Products Transfusion (3 forms) from patient or LAR – study coordinators will assist with this
6. Place Epic order for "Transfuse FFP" when ready for transfusion and call Blood Bank to proceed with transfusion

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.
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.
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4. Shen C, et al. Treatment of 5 Critically Ill Patients WithCOVID-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

Tocilizumab (IL-6 Blockade)

Studies have shown that a cytokine storm contributed to the pathogenesis of two diseases caused by other coronaviruses, SARS and MERS. In COVID-19, higher plasma levels of cytokines and other inflammation-mediating chemical messengers were found in patients requiring intensive care unit-level care. Among these, G-CSF and IL-6 have been identified as the key cytokines leading to the inflammatory storm that may result in increased alveolar-capillary blood-gas exchange dysfunction and lead to pulmonary fibrosis and organ failure in COVID-19.[1-4]

Tocilizumab is a recombinant humanized monoclonal antibody against IL-6 receptor. It is indicated for rheumatoid arthritis, other rheumatologic disorders, and for cytokine release syndrome (CRS).[5] A retrospective study from China evaluated the use of tocilizumab in patients with COVID-19 and demonstrated resolution of fever and decreased oxygen requirements.[6] To date, no randomized trials have been published. It is important that clinicians, patients, and family members recognize the safety and effectiveness of tocilizumab for COVID-19 are not known at this time and that this is an experimental therapy. **Use of this agent should be prioritized to the ongoing DH clinical trial.** The following information is intended to serve as a resource for clinicians considering use of tocilizumab outside of the ongoing trial.

Criteria for Use of Tocilizumab

SARS-CoV-2 positive requiring ICU-level care

AND

Lack of clinical improvement [(a)] not attributable to other etiologies despite receiving the appropriate standard of care[(b)]

↓

If febrile (at least one or more temperature ≥38.5℃) daily for three consecutive days

AND

Laboratory findings[(b)] highly suggestive of cytokine release syndrome

AND

Hypotension (systolic blood pressure <90 mmHg) requiring vasopressor support

OR

Hypoxia (SpO2 ≤90%) requiring mechanical ventilation with persistent FiO2 ≥40% OR PaO2/FiO2 <300 mmHg

OR

Chest imaging consistent with lung disease progression

↓

Give tocilizumab 400 mg IV once

(requires ID Consult approval)

(a) Lack of clinical improvement is defined as: unchanged or worsened oxygen requirements, hemodynamic instability with unchanged or increased vasopressor requirements, findings suggestive of organ damage such as acute kidney injury or acute liver injury, clinical signs/symptoms associated with cytokine release syndrome unrelated to another etiology (Supplemental Table 1)

(b) Standard of care is defined as the indicated supportive care measures for the individual patient and, if applicable, receiving drug therapy for COVID-19 in accordance to the institutional guidance

(c) Laboratory tests to evaluate risk for cytokine release syndrome: D-dimer >1.00 mcg/mL, CRP >10 mg/L either uptrending OR persistently elevated, high-sensitivity cardiac troponin-I >28 pg/mL, ferritin >365 ng/mL

EXCLUSION CRITERIA for tocilizumab

- Age <18 y.o.
- AST or ALT >5x ULN
- ANC <500 cells/mL
- Platelet levels <50,000 cells/mL
- Complicated diverticulitis or intestinal perforation
- Concurrent bacterial or fungal infection

Supplemental Table 1: Clinical signs and symptoms associated with cytokine release syndrome

Organ system	Symptoms
Constitutional	Fever+/- rigors, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia +/- bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

References:

1. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020; 395(10223):507-513.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395:497-506.
3. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. *BioRxiv*. 2020: 2020.02.12.945576. DOI: https://doi.org/10.1101/2020.02.12.945576.
4. Lee DW, Gardner R, Porter DL, et l. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014; 124(2): 188-195.
5. ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use. [Package insert]. Revised 06/019. Genentech, Inc. San Francisco, CA. Accessed on 3/22/2020 from: https://www.gene.com/download/pdf/actemra_prescribing.pdf
6. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *chinaXiv*:202003.00026v1.

CONSIDERATIONS FOR CERTAIN CONCOMITANT MEDICATIONS IN COVID-19 PATIENTS

Medication	Action
ACE-I or ARBs	• Continue or start only in patients meeting an indication for use (e.g. cardiovascular disease) • DO NOT START solely and specifically for the treatment of COVID-19
Statins	• Continue or start only in patients meeting an indication for use (e.g. prevention of cardiovascular disease) • DO NOT START solely and specifically for the treatment of COVID-19
NSAIDS	• Continue or start only in patients meeting an indication for use (e.g. co-morbid condition) • NO DIFFERENCE between acetaminophen or NSAIDS as antipyretic strategies between patients with or without COVID-19
Vitamins/Supplements (e.g. vitamin C, zinc)	• 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.)

*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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- Bancos S, Bernard MP, Topham DJ, Phipps RP. Ibuprofen and other widely used non-steroidal anti-inflammatory drugs inhibit antibody production in human cells. *Cell Immunol*. 2009;258(1):18-28. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19345936.
- Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19.
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