Dayton Children's Hospital Guidance for Use of Remdesivir and for Convalescent Plasma in Hospitalized Patients with COVID-19

(**Note**: Formal Infectious Disease consultation is required prior to dispensation of either remdesivir and/or convalescent plasma)

Remdesivir

Remdesivir is an adenosine nucleotide-analog inhibitor of RNA-dependent RNA polymerases, whose mechanism of action causes resultant premature termination of viral RNA transcription [1]. It is an antiviral agent with *in vitro* activity against multiple RNA viruses, including SARS-Co-V-2. On 5/1/20, the FDA issued an Emergency Use Authorization (EUA) allowing remdesivir use for treatment of adult and pediatric patients hospitalized with severe illness caused by COVID-19, with severe disease defined as those patients with: $\leq$ 94% oxygen saturation (SpO_2) on room air, a need for supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation (ECMO)[2,3]. Preliminary results of a phase 3, randomized, double-blind, placebo-controlled trial of remdesivir involving 1,059 hospitalized adults $\geq$ 18 years (mean age [years] $\pm$ SD, 58.9 $\pm$ 15.0) published in May 2020 showed a shortened time to recovery in the group treated with remdesivir (11 days, 95% CI, 9-12) compared to placebo (15 days, 95% CI, 13-19)[4]. The final report from this trial (ie, the Adaptive COVID-19 Treatment Trial, or ACTT-1) was published in October 2020 [5]. The final report reiterated that patients in the remdesivir group had a shorter observed time to clinical recovery compared to those in the placebo group (median of 10 days versus 15 days, rate ratio for recovery, 1.29; 95% CI, 1.12-1.49; $p < 0.001$). The observed benefits of remdesivir were most apparent in individuals requiring low-flow supplemental oxygen at baseline (as opposed to those requiring high-flow supplemental oxygen, mechanical ventilation, or ECMO), as well as in individuals randomized $\leq$ 10 days following the onset of symptoms. All-cause mortality was 11.4% with remdesivir versus 15.2% with placebo (hazard ratio 0.73; 95% CI, 0.52-1.03), while the percentages of overall adverse effects were similar between the two groups.

Results of a separate phase 3, randomized, open-label trial evaluating the efficacy and adverse effects of 5 vs. 10 days of remdesivir (initiated on day 1 of hospitalization) vs. standard care in 584 hospitalized individuals with moderate COVID-19 pneumonia (defined as the presence of pulmonary infiltrates on imaging and $SpO_2 > 94\%$ on room air) were published in August 2020 [6]. Individuals $\geq$ 12 years who fulfilled all other enrollment criteria were eligible for study inclusion, though the reported median ages (in years)(IQR) for the groups were 56 (45-66) for the 10-day remdesivir group, 58 (48-66) for the 5-day remdesivir group, and 57 (45-66) for the standard care group. Those in the 5-day treatment group showed a statistically significant difference in improved clinical status at 11 days compared to those who received standard care, which was noted by the study authors to be of uncertain clinical importance. The 10-day treatment group showed no significant difference at 11 days compared to the standard care group. The difference in adverse events (most frequently nausea, hypokalemia and headache)

between the 10-day treatment group and the standard care group was found to be significant (12%; 95% CI, 1.6 – 21.8%; p=0.02), though the difference in adverse events between the 5-day treatment group and standard care group was not significant.

In the preliminary published results from the large-scale, randomized, open-label study of 4 antiviral agents (including remdesivir) undertaken by the World Health Organization (the Solidarity trial), 2,743 individuals receiving remdesivir were compared with 2,708 controls (receiving standard of care treatment) in an intention-to-treat analysis [7]. This study found no differences in the overall mortality rates for those receiving remdesivir versus controls (remdesivir death rate ratio 0.95; 95% CI, 0.81-1.11; p=0.5). Available results from this trial also demonstrated that remdesivir receipt did not: a) decrease initiation of mechanical ventilation for hospitalized patients who were not already mechanically ventilated or b) shorten time to hospital discharge (relative to controls).

Based heavily on the preliminary results of the ACTT-1 trial and data from Spinner et al [4,6], on 8/28/20 the FDA revised and expanded the scope of authorized uses under the remdesivir EUA to include treatment of all hospitalized adult and pediatric patients with suspected or laboratory-confirmed COVID-19, regardless of disease severity [8]. Following the October 2020 publication of final results from the ACTT-1 trial, on 10/22/20 the FDA approved the use of remdesivir for treatment of COVID-19 in hospitalized individuals $\geq$ 12 years [9]. At the present time, there are no large-scale published studies evaluating the safety, tolerability, pharmacokinetics, and efficacy of remdesivir in children < 18 years with COVID-19. However, an open-label phase 2/3 clinical trial evaluating these factors was initiated on 6/16/20 and is currently ongoing. For children < 12 years, remdesivir continues to remain available under the FDA EUA [10].

Most reported COVID-19 infections in children < 18 years are asymptomatic or mildly symptomatic, and overall COVID-associated hospitalization rates in children are low [11,12]. However, approximately 1/3 of children admitted to the hospital with symptomatic COVID-19 will require ICU-level care, and a small subset of pediatric patients with COVID-19 can develop respiratory failure, ARDS and associated multi-organ failure [11,13]. Consideration for remdesivir use should currently be reserved for such inpatients (ie, and ***not*** for all hospitalized patients) pending availability of more large-scale pediatric-focused trials which support broader remdesivir usage.

Dayton Children's Hospital Eligibility Criteria for Inpatient Remdesivir Receipt:

1. #Active COVID-19 disease – defined as laboratory-confirmed infection via PCR testing within 14 days of admission
2. $SpO_2 \leq 94\%$ on room air *or* requiring supplemental oxygen (via nasal cannula, high-flow nasal cannula, face mask, or NIMV) *or* requiring mechanical ventilation *or* requiring ECMO

Exclusion Criteria

1. Baseline ALT > 5 times the upper limit of normal for age

2. ALT elevation plus signs/symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase or INR
3. Patients > 28 days old with eGFR < 30 mL/min, and full-term neonates (≥ 7 and ≤ 28 days old) with serum creatinine ≥ 1 mg/dL – unless the potential benefit outweighs the potential risk
4. Patient weight < 3.5 kg

[#]Remdesivir use for inpatients highly suspected of having COVID-19 and with negative PCR testing will be considered on an individual case-by-case basis

Additional Resources:

- Information from NIH regarding Antiviral Agents Approved or Under Evaluation for COVID-19 (including remdesivir): https://www.covid19treatmentguidelines.nih.gov/tables/table-2/

REMDESIVIR

Patient with active COVID-19 disease – defined as laboratory-confirmed infection via PCR testing within 14 days of admission*

AND

SpO2 ≤94% on room air **OR** requiring supplemental oxygen (via nasal cannula, high flow nasal cannula, face mask, or NIMV) **OR** requiring mechanical ventilation **OR** requiring ECMO

*Inpatients highly suspected of having COVID 19 with negative PCR testing will be considered on an individual case-by-case basis

Yes

No → Consider alternative diagnosis and therapy

Baseline ALT > 5 times the upper limit of normal for age

OR

ALT elevation plus signs and symptoms of liver inflammation or increasing direct bilirubin, alkaline phosphatase or INR

OR

Patient > 28 days old with eGFR < 30 ml/min, full-term neonate (≥7 and ≤28 days old) with serum creatinine ≥1 mg/dl – unless the potential benefit outweighs the potential risk

OR

Patient weight < 3.5 kg

Yes → Obtain ID consult **without** consideration for remdesivir

No → Obtain ID consult **with** consideration for remdesivir

Patient ≤ 12 years of age or weight < 40 kg

Yes → ID to discuss risks/benefits of remdesivir use with parent/caregiver/patient and provide a copy of the EUA fact sheet (https://www.fda.gov/media/137565/download).

ID to discuss risks/benefits of remdesivir use with parent/caregiver/patient and provide a copy of the EUA fact sheet (https://www.fda.gov/media/137565/download).

No → ID to discuss risks/benefits of remdesivir use with parent/caregiver/patient.

Remdesivir ordered, prepared, dispensed, and administered per EUA guideline (https://www.fda.gov/media/137566/download).

Remdesivir ordered, prepared, dispensed, and administered per FDA prescribing information (https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf).

Obtain baseline serum creatinine, BUN, AST, ALT, alkaline phosphatase, and bilirubin levels and order daily testing of these labs for as long as the patient is on remdesivir.

Last updated: February 9, 2021

Convalescent Plasma

COVID-19 convalescent plasma (CP) is human plasma (i.e., the aqueous component of blood) collected from individuals whose plasma contains high titers of anti-SARS-CoV-2 antibodies. Use of CP has previously been trialed for treatment of other coronaviruses, including MERS and SARS [12]. An Expanded Access Program (EAP) for CP sponsored by the Mayo Clinic was established in April 2020 in order to facilitate access to CP for hospitalized individuals > 18 years old with laboratory-confirmed COVID-19 and severe/life-threatening infection (or who were judged by a treating provider to be at high risk for progression to severe or life-threatening disease). Data collected from the initial 20,000 recipients of CP from the EAP found low overall rates of serious adverse events, with the rates of transfusion reactions and thromboembolic/thrombotic events both < 1%. Cardiac events occurred in 3% of CP recipients [14].

On 8/23/20, the FDA approved an EUA request for use of COVID-19 CP as a passive immune therapy for hospitalized patients with COVID-19. Justification for the CP EUA was based on 4 factors: 1) a history of use of CP for other coronaviruses, 2) evidence of preclinical safety and efficacy in animal models, 3) data on safety and efficacy provided by the EAP sponsored by the Mayo Clinic, and 4) published studies including multiple case series, retrospective matched cohort studies, 3 small non-randomized controlled trials (with controls based on a lack of plasma availability), and 2 small randomized controlled trials - one from Wuhan, China that was stopped early due to low enrollment [15] and another from the Netherlands that was also discontinued early due to observation of high anti-SARS-CoV-2 antibodies in recipients prior to transfusion [16]. On 2/4/21, the FDA issued a revised EUA for COVID-19 CP. The revised EUA authorizes use of only high-titer COVID-19 CP. Additionally, the use of high-titer COVID-19 CP is limited to inpatient administration early in the course of disease or when administered to patients with impaired humoral immunity [17]. The term 'early in the course of disease' is defined by the revised EUA as "prior to respiratory failure requiring intubation and mechanical ventilation." [18]

To date, there have been only two publications in the medical literature that report the use of COVID-19 CP transfusions for pediatric patients [19, 20]. As of September 1, 2020, there are two active pediatric-focused Phase 1 clinical trials in the U.S. investigating the safety of CP administration in children with SARS-CoV-2 infection (https://clinicaltrials.gov/ct2/results?term=convalescent&cond=COVID-19&recrs=a&age_v=&age=0&gndr=&type=&rslt=&Search=Apply). One of these trials (which is based out of Johns Hopkins Hospital) is currently enrolling individuals between the ages of 1 month – 18 years with confirmed infection and one of the following: immunocompromise, hemodynamically significant heart disease, lung disease with chronic respiratory failure, or age ≤ 1 year.

As per the FDA, "Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population has not been evaluated. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on individualized assessment of risk and benefit."[18]

Given the: 1) current lack of data on CP use in the pediatric population, 2) Infectious Diseases Society of America's statement that **"…**continued collection of data in randomized clinical trials [is needed] to better understand the benefits of convalescent plasma treatment before authorizing its wider use in patients with COVID-19"[21] and 3) theoretical and known potential side effects associated with CP use (including but not limited to: transmission of infectious pathogens, allergic reactions, hemolytic reactions, transfusion-associated cardiac overload [TACO], transfusion-related acute lung injury [TRALI] and antibody-dependent enhancement of infection) [18], consideration of CP use for inpatients at Dayton Children's Hospital should currently be reserved for individuals meeting the following inclusion criteria.

Dayton Children's Hospital Eligibility Criteria for Inpatient COVID-19 Convalescent Plasma Receipt:

1. #Active COVID-19 disease – defined as laboratory-confirmed infection via PCR testing within 7 days of admission
2. Critical/life-threatening COVID-19 disease *or* at high risk for progression to critical or life-threatening disease with evidence of hyperinflammation (Table 1) [13]
3. Failure to achieve appreciable clinical benefit despite treatment with other potentially therapeutic agents *or* if other potentially therapeutic agents are contraindicated

#Convalescent plasma use for inpatients highly suspected of having COVID-19 and with negative PCR testing will be considered on an individual case-by-case basis.

Exclusion criteria:

1. Patients who are intubated and mechanically ventilated due to respiratory failure associated with acute COVID-19 infection (with the sole exception being the subgroup of these patients who also have impaired humoral immunity)
2. Patients with a history of severe allergic reactions or anaphylaxis to transfusion of blood products (including but not limited to plasma)
3. Extreme caution is advised with administration of CP to individuals with pre-existing co-morbidities (such as severe liver or kidney disease/failure) that could predispose to an increased risk of thrombosis/thromboembolic events
4. Caution is advised with administration of CP to individuals with impaired cardiac function or heart failure – if CP is administered to these patients, then use of smaller volumes or more prolonged transfusion times may be necessary.

COVID-19 CONVALESCENT PLASMA

Active COVID-19 disease – defined as laboratory–confirmed infection via PCR testing within 7 days of admission*
AND
Critical/life-threatening COVID-19 disease OR at high risk for progression to critical or life-threatening disease **with** evidence of hyperinflammation (Table1)[13]
AND
Failure to achieve appreciable clinical benefit despite treatment with other potentially therapeutic agents OR if other potentially therapeutic agents are contraindicated.

*Convalescent plasma use for inpatients highly suspected of having COVID 19 and with negative PCR testing will be considered on an individual case-by-case basis.

Yes

No → Consider alternative diagnosis and treatment

Patient intubated/mechanically ventilated due to respiratory failure from COVID-19

No

Yes

Patient with impaired humoral immunity

No → Consider alternative treatment

Yes

Patient with history or severe allergic reactions or anaphylaxis to transfusion of blood products (including but not limited to plasma).

Yes → Obtain ID consult **without** consideration for convalescent plasma

No → Obtain ID consult **with** consideration for convalescent plasma

Patient with pre-existing comorbidities (such as severe liver or kidney disease/failure) that could predispose to an increased risk of thrombosis

Patient has impaired cardiac function or heart failure

Yes → Proceed with caution to treatment with convalescent plasma. Smaller volumes or prolonged infusion times may be necessary if patient has impaired cardiac function or heart failure.

No → Obtain signed consent for convalescent plasma and store on media tab in EPIC

Obtain baseline CBC with differential, PT/INR, PTT, fibrinogen, D-dimer, BUN, serum creatinine, AST, ALT, bilirubin level and SARS-CoV-2 IgG. **DO NOT** administer convalescent plasma if SARS-CoV-2 IgG is positive!

Obtain and administer convalescent plasma per EUA provider fact sheet at https://www.fda.gov/media/141478/download. For patients > 40 kg, recommended dose is 200-500 ml; for patients ≤40 kg, recommended dose is 10-15 ml/kg.

Report all convalescent plasma adverse events to the FDA.
FDA recommends the measurement of neutralizing antibody titers when/if available.

Last updated: February 9, 2021

References

1. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Available at: www.idsociety.org/COVID19guidelines. Accessed August 31, 2020.
2. FDA. Coronavirus (COVID-19) update: FDA issues emergency use authorization for potential COVID-19 treatment. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Accessed August 31, 2020.
3. FDA. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Remdesivir (GS-5734™). Accessed July 7, 2020.
4. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of COVID-19 – Preliminary Report. *N Engl J Med*. 2020 May 22; NEJMoa2007764. doi: 10.1056/NEJMoa2007764. Online ahead of print.
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of COVID-19 – Final Report. *N Engl J Med*. 2020. 383: 1813-1826.
6. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs. Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020 Aug 21; e2016349. doi: 10.1001/jama.2020.16349. Online ahead of print.
7. WHO Solidarity Trial Consortium. Repurposed antiviral drugs for covid-19—interim WHO Solidarity trial results. *medRxiv* 15 Oct 2020. doi: 10.1101/2020.10.15.20209817.
8. FDA. COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/covid-19-update-fda-broadens-emergency-use-authorization-veklury-remdesivir-include-all-hospitalized. Accessed September 1, 2020.
9. FDA. FDA News Release: FDA Approves First Treatment for COVID-19. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19.
10. FDA. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of VEKLURY® (remdesivir) for Hospitalized Pediatric Patients Weighing 3.5 kg to Less than 40 kg or Hospitalized Pediatric Patients Less Than 12 Years of Age Weighing at Least 3.5 kg. Accessed November 10, 2020.
11. Kim L, Whitaker M, O'Halloran A, et al. Hospitalization Rates and Characteristics of Children Aged < 18 Years Hospitalized with Laboratory-Confirmed COVID-19 – COVID-NET, 14 States, March 1-July 25, 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69: 1081-1088.
12. Shane AL, Sato AI, Kao C, et al. A Pediatric Infectious Disease Perspective of SARS-CoV-2 and COVID-19 in Children. *J Pediatric Infect Dis Soc*. 2020 Aug 25:piaa099. doi: 10.1093/jpids/piaa099. Online ahead of print.
13. Dulek DE, Fuhlbrigge RC, Tribble AC, et al. Multidisciplinary Guidance Regarding the Use of Immunomodulatory Therapies for Acute COVID-19 in Pediatric Patients. *J Pediatric Infect Dis Soc*. 2020 Aug 18;piaa098. doi: 10.1093/jpids/piaa098. Online ahead of print.
14. FDA. Clinical Memorandum re: EUA 26382: Emergency Use Authorization (EUA) Request for COVID-19 Convalescent Plasma. Available at: https://www.fda.gov/media/141480/download. Accessed August 31, 2020.

15. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19: A Randomized Clinical Trial. *JAMA*; 324(5): 460-470.
16. Gharbharan A, Jordans CCE, Geurtsvankessel C, et al. Convalescent Plasma for COVID-19. A Randomized Clinical Trial. *medRxiv*, 2020: p. 2020.07.01.20139857. doi: https://doi.org/10.1101/2020.07.01.20139857
17. FDA. Letter of Authorization, Reissuance of Convalescent Plasma EUA. February 4, 2021. Available at: https://www.fda.gov/media/141477/download. Accessed February 8, 2021.
18. FDA. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients. Accessed February 8, 2021.
19. Figlerowicz M, Mania A, Lubarski K, et al. First Case of Convalescent Plasma Transfusion in a Child with COVID-19-associated Severe Aplastic Anemia. *Transfus Apher Sci* 2020: 102866.
20. Diorio C, Anderson EM, McNerney KO, et al. Convalescent Plasma for Pediatric Patients with SARS-CoV-2-associated Acute Respiratory Distress Syndrome. *Pediatr Blood Cancer*. 2020; 67: e28693.
21. Response from IDSA President to Announcement of Emergency Use Authorization for Convalescent Plasma to Treat COVID-19. Available at: https://www.idsociety.org/news--publications-new/articles/2020/response-from-idsa-president-to-announcement-of-emergency-use-authorization-for-convalescent-plasma-to-treat-covid-19/ Accessed September 1, 2020.

Table 1	
Characteristic	**Comments**
Evidence for Hyperinflammatory State	
Clinical Signs: Sustained or recurrent fever Hepatomegaly Splenomegaly and /or lymphadenopathy	Fever is likely most informative in the setting of other features of hyperinflammation described below Consider evaluation for concurrent viral, bacterial, or fungal infection
Laboratory: Elevated ferritin and/or CRP Decreased fibrinogen Elevated serum IL-6 or other pro-inflammatory cytokines Other CSS associated labs (elevated sIL2R, sCD163, or triglycerides)	Very likely to be non-specific in isolation Specific values indicating need for immunomodulation are not currently known Many labs will not have clinically actionable turnaround time for serum cytokines and some CSS associated labs
Rapid deterioration and/or Presence or risk for Organ Failure	
Cardiac: Elevated BNP or troponin Persistent hemodynamic instability nonresponsive to standard pressor support Elevated lactate after appropriate fluid resuscitation Evidence of cardiomyopathy by echocardiogram Life threatening arrhythmias	Evaluation for confounding causes of organ dysfunction or failure (e.g. other infections, medication effects, etc.) Attention should be given to the pace of clinical worsening. Patients progressing rapidly to severe COVID 19 may be at risk for further progression to critical COVID 19.

Respiratory: Abnormal PaO2/FiO2 ratio or SpO2/FiO2 Rapidly escalating supplemental oxygen requirement ***New mechanical ventilation requirement	
Coagulopathy: Elevated D-dimer Thrombocytopenia Prolonged PT or PTT Decreased fibrinogen	
Neurologic: Altered mental status	
Hepatic: Evidence of coagulopathy (see above) Elevated bilirubin, GGT, and /or transaminases	
Renal: Decreased creatinine clearance	
Abbreviations: BNP, brain natriuretic peptide; CRP, C-reactive protein; CSS, cytokine storm syndrome; PT, prothrombin time; PTT, partial thromboplastin time; GGT, gamma-glutamyl transferase ***Only if the patient also has known impaired humoral immunity	