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Question or request:

1. What is the role of convalescent plasma treatment for COVID-19 patients?
2. When might COVID-19 Convalescent Plasma (CCP) treatment become available?
3. How can facilities obtain CCP?
4. Which patients are most likely to benefit from CCP Transfusion?
5. What is the optimal dose of CCP?

Recommendation/s in bullet form:

1. In August 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of convalescent plasma for the treatment of hospitalized patients with COVID-19.
2. The use of COVID-19 Convalescent Plasma (CCP) collected from individuals who have recovered from COVID-19 is being implemented at hospitals in New Mexico as one potential treatment option.
3. Based on available data, the MAT cannot recommend for or against CCP use.
4. Randomized controlled trials have not yet shown a clinically significant benefit from CCP. However, matched-control studies suggest that a mortality benefit may be seen if high-titer CCP is transfused early in the patient's clinical course (either within 72 hours of diagnosis or within 72 hours of admission).
5. If CCP will be transfused, the MAT recommends only doing so if administered within 72 hours of the patient's first COVID admission.
6. The optimal dose of CCP (1 unit vs 2 units) is not yet known. Until the state and national supply of CCP increases, transfusion of 1 unit per patient is recommended so more patients have access to the therapy.
7. Clinicians may order CCP from their hospital's blood bank using locally established procedures.
8. In order for the patient to receive CCP through the EUA, they must be consented for blood using their local hospital's policies and procedures and be provided with the "FDA CCP Fact Sheet for Patients/Caregivers."

Assessment:

In August 2020, the FDA issued an EUA for the use of CCP for the treatment of hospitalized patients with COVID-19.¹ CCP is plasma collected from individuals who have recovered from COVID-19 and contains antibodies to SARS-CoV-2. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2009-2010 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic.^{2,3,4}

As of October 2020, four randomized controlled trials (RCTs) of CCP have been published.^{5,6,7,8} Three were stopped early due to lack of enrollment^{5,6} or concern for lack of benefit given that many of the patients already had detectable COVID-19 antibodies at the time of enrollment.⁷ The most recent RCT did not demonstrate a reduction in progression to severe COVID-19 or all-cause mortality.⁸ However, this trial was not designed to detect any differences when CCP is transfused very early in the patient's clinical course, and many of the patients received CCP with low levels of antibodies.

One retrospective study identified a mortality benefit when CCP is transfused within 3 days of diagnosis compared to greater than 3 days of diagnosis (21.6% vs 26.7% at 30 days).⁹ A prospective, propensity score-matched study comparing CCP vs standard of care demonstrated a mortality benefit when high-titer CCP is transfused within 72 hours admission (1.2% vs 7.0% at 28 days).¹⁰

Clinical trials are ongoing to assess the use of high-titer CCP for inpatients, in the emergency department, and in outpatient settings.

The MAT agrees with the National Institute of Health (NIH) by neither recommending for or against the use of CCP for treatment of COVID-19.¹¹ However, if CCP is to be transfused, the MAT recommends only transfusing 1 unit of CCP for hospitalized patients with confirmed COVID-19 within 72 hours of admission. Judicious use of CCP is important as the inventory is constantly fluctuating.

ABO-incompatible CCP may be deemed acceptable with Clinical Pathologist and/or institutional/medical director approval on a case-by-case basis.

Clinicians may order CCP from their hospital's blood bank using locally established procedures. In order for the patient to receive CCP through the EUA, they must be consented for blood using their local hospital's policies and procedures and be provided with the "FDA CCP Fact Sheet for Patients/Caregivers" (<https://www.fda.gov/media/141479/download>).

New Mexico Convalescent Plasma Treatment

Most of the hospital systems in New Mexico have used CCP. Both the Presbyterian and Lovelace healthcare systems have transfused CCP under the FDA EUA while UNMH is participating in multiple clinical trials.

Red flags and Concerns:

While treatment with CCP has been shown to be safe in published studies, it is not without risk. As with other blood transfusions, common risks include allergic transfusion reactions, febrile non-hemolytic transfusion reactions, and volume overload. Very rarely, inadvertent infection with another infectious disease agent and hemolytic transfusion reactions may occur. Many of these risks are mitigated with the modern blood banking techniques used to screen for blood-borne pathogens and match the blood type of donors and recipients, so this risk is considered very low. There is a higher risk, however, of transfusion-related acute lung injury (TRALI). Blood centers have worked to mitigate the risk of TRALI as much as possible by only collecting from either female donors without HLA antibodies or male donors. This risk should be considered in the risk-benefit assessment for each patient.

There is also the theoretical risk of causing antibody-dependent enhancement of infection (ADE), which can enhance the disease in the presence of certain antibodies.¹² Since the proposed use of CCP in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, this risk is thought to be low. Additionally, there is a risk that antibody administration to those exposed to SARS-CoV-2 may prevent disease by attenuating the immune response, leaving individuals vulnerable to subsequent reinfection. While additional studies are needed, if this risk proves real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

Given the high mortality of COVID-19, particularly among the elderly and vulnerable individuals, the potential benefits are thought to outweigh the risks in those who are hospitalized and receive CCP early in their clinical course. However, a risk-benefit assessment should be conducted for all cases where CCP administration is considered.

Contributors:

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Resources/Reference:

¹ U.S. Food and Drug Administration Revised Information for Investigational COVID-19 Convalescent Plasma Available from: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma> [Accessed November 9, 2020].

² Cheng, Y., Wong, R., Soo, Y. O. Y., Wong, W. S., Lee, C. K., Ng, M. H. L., ... & Cheng, G. (2005). Use of convalescent plasma therapy in SARS patients in Hong Kong. *European Journal of Clinical Microbiology and Infectious Diseases*, 24(1), 44-46.

³ Chen, L., Xiong, J., Bao, L., & Shi, Y. (2020). Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases*, 20(4), 398-400.

⁴ Van Griensven, J., Edwards, T., de Lamballerie, X., Semple, M. G., Gallian, P., Baize, S., ... & Lomas, C. (2016). Evaluation of convalescent plasma for Ebola virus disease in Guinea. *New England Journal of Medicine*, 374(1), 33-42.

- ⁵ Li, L. et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-threatening COVID-19. *JAMA*. 2020; 324(5): 460-70.
- ⁶ Avendano-Sola, C., et al. Convalescent Plasma for COVID-19: A multicenter, randomized clinical trial. **[Preprint]**. September 29, 2020. <https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v3>
- ⁷ Gharbharan, A., et al. Convalescent Plasma for COVID-19. A Randomized Clinical Trial. **[Preprint]**. July 3, 2020. <https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1>
- ⁸ Agarwal, A, et al. Convalescent plasma in the management of moderate COVID-19 in adults in India: Open label phase II multicenter randomized controlled trial (PLACID Trial). *BMJ*. 2020; 371:m3939.
- ⁹ Joyner, M., et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. **[Preprint]**. August 12, 2020
- ¹⁰ Salazar, E., et al. Treatment of Coronavirus Disease 2019 Patients with Convalescent Plasma Reveals a Signal of Significantly Decreased Mortality. *American Journal of Pathology*. 2020; 190 (11): 2290-2303.
- ¹¹ Convalescent Plasma. COVID-19 Treatment Guidelines. <https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma/> [Accessed November 9, 2020]
- ¹² Casadevall, A., & Pirofski, L. A. (2020). The convalescent sera option for containing COVID-19. *The Journal of clinical investigation*, 130(4).