Blood Bulletin
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COVID-19 Convalescent Plasma - a Potentially Effective Therapeutic Modality

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Key Points

- Convalescent plasma collected from patients who have recovered from COVID-19 offers a potentially safe and effective, but unproven therapeutic modality.
- Currently, there are no FDA approved therapies for COVID-19, but small uncontrolled case series report improvement in patient outcomes using convalescent plasma.
- FDA requires the clinical application of COVID-19 convalescent plasma to be conducted under one of three defined pathways.
- COVID-19 convalescent plasma collection is a collaborative effort between the blood center, hospital, physicians and public health.

Background: SARS-CoV-2, the virus causing COVID-19, was first recognized in Wuhan, China in December 2019. Subsequently, it has developed into a global health crisis due to a high rate of transmission and significant morbidity and mortality in older individuals and those with underlying health conditions.

Role of Convalescent Plasma: COVID-19 currently has no proven treatment. The infusion of antibody-rich plasma from recovered COVID-19 patients is one option, which is projected to be a safe and potentially effective therapy for treatment and/or post exposure prophylaxis. In the past, few controlled trials have been performed to evaluate the efficacy of convalescent plasma, in large part due to its emergency application in times of epidemics. Suggestive evidence[1] for the benefit of convalescent plasma for treatment or prophylaxis of other infectious diseases has been documented for H1N1 influenza in 2009 and coronaviruses that caused severe acute respiratory syndrome (SARS) in 2002-2003 and Middle East respiratory syndrome (MERS) in 2012. Treatment is based on the function of antibodies, which will neutralize the virus and prevent further replication and disease-related tissue damage. Experience from SARS suggests that convalescent plasma contains neutralizing antibodies.[2] In a 2020 uncontrolled series of five critically ill patients from China with COVID-19, administration of COVID-19 convalescent plasma (CCP) was followed by clinical improvement.[3] In another uncontrolled pilot study of 10 patients from China with severe COVID-19, CCP doses of 200mL with neutralizing antibody titers >1:640 dilution were temporally associated with improvement in symptoms without serious adverse effect in the recipients.[4] Data are limited and clinical outcome results are likely to be published; hence no efficacy claims are yet justified for this product.

Pathways for Clinical Application of CCP: On March 24, 2020, the United States Food and Drug Administration (FDA) published the initial recommendations for the use of CCP which were subsequently updated.[5] There are three pathways for clinical application of CCP. The first is under an emergency use investigational new drug (eIND) application allowing compassionate use in an individual patient with severe or immediately life-threatening COVID-19. The second pathway is to apply for an IND to support research, which is the traditional approach for clinical trials. The third pathway is a government-led initiative providing expanded access program (EAP) IND to participating institutions under a master treatment protocol with modest data reporting requirements.[6]

Mayo Clinic is the lead institution in the EAP IND for hospitalized patients with defined severe or life-threatening COVID-19.[7] This study protocol will enable the collection of extensive data through a non-randomized study design and can be accessed at: https://www.uscovidplasma.org/.

Current Clinical Trials: Currently many clinical trials have been proposed to evaluate CCP for the prevention and treatment of COVID-19 on ClinicalTrials.gov.[8] A representative sample of such studies were summarized by Bloch[9] as follows:

- Use of CCP as post-exposure prophylaxis among adults who have had close contact exposure to COVID-19 but have not yet manifested symptoms of COVID-19 disease.
- Evaluation whether CCP can help patients initially presenting with mild disease and confirmed SARS-CoV-2.
- A study of CCP in moderately ill patients, hospitalized but not of sufficient acuity to warrant intensive care unit admission or mechanical ventilation.
- Evaluate CCP as a rescue intervention in patients who require mechanical ventilation due to COVID-19.
- Evaluate safety and pharmacokinetics of CCP in high-risk pediatric patients.

Patient Eligibility: The decision to administer CCP relies on the judgement of the treating clinicians. The table below shows criteria used with patients in current protocol or published studies.

Mayo EAP Institutional Review Board (IRB)[7] Severe COVID-19 (one or more)	**Mayo EAP IRB[7] Life-threatening COVID-19 (one or more)**	***JAMA* Study Five Patients[3]**	***PNAS* Study Ten Patients[4]**
Dyspnea Respiratory Rate ≥30/min	Respiratory Failure	Severe Pneumonia with Rapid Progression and High Viral Load Despite Anti-Viral Treatment	Respiratory Distress Respiratory Rate ≥30/min
Blood Oxygen Saturation ≤93%	Septic Shock	Currently or Previously Received Mechanical Ventilation	Oxygen Saturation Level <93% at rest
PAO_2/FIO_2 <300	Multiple Organ Dysfunction or Failure	PAO_2/FIO_2 <300	PAO_2/FIO_2 <300
Lung Infiltrates >50% Within 24 - 48 Hours			

Transfusing Convalescent Plasma: The ordering provider will be notified once the CCP is received by the hospital blood bank. CCP should be ABO compatible (i.e. Type O plasma is only given to a Type O patient) per hospital and blood center policy. Considerations should be given for non-ABO compatible CCP transfusion if the clinical benefit outweighs the risk. One must ensure the treating clinicians understand using non-ABO compatible plasma may violate the hospital IND so a request for deviation from current protocol or application for an eIND should be in place prior to the transfusion event. Transfusion of CCP should follow hospital policy for plasma administration. CCP dose is generally one to two units per patient; each unit is approximately 200mL, administered at a transfusion rate of 100 to 250mL/hour or per hospital policy. After thaw, CCP may be stored for up to five days at 1-6 °C. Possible adverse events are the same as other plasma products and may include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), allergic and febrile reactions. In two small studies involving 15 patients, one patient exhibited a transient facial red spot and no serious adverse events.[3,4]

Response Assessment: This varied between the studies — a summary is provided in the table below. It should be noted that CCP is a temporary bridge therapy in anticipation for approval of hyperimmune globulin being developed by plasma fractionators. This will be a lower volume, virally inactivated product with known quantity of SARS-CoV-2 antibodies.

Mayo EAP IRB[7]	***JAMA* Study Five Patients[3]**	***PNAS* Study Ten Patients[4]**
Number of Days on Mechanical Ventilation	Four - Normalization of Body Temperature	All - Resolution of Symptoms: Fever, Cough, Shortness of Breath, and Chest Pain
Acute Care Facility Length of Stay	Four - SOFA score decreased*	All – Varying Degrees of pulmonary lesion adsorption
Number of Days in Intensive Care Unit	Three - Weaned from Mechanical Ventilation	Two of Three - Weaned from Mechanical Ventilator Varying degrees of absorption of lung lesions within seven days
Survival Until Discharge from an Acute Care Facility	Four - PAO_2/FIO_2 Increased	Most Patients - Increased SaO_2
	Three - Discharged Two - Stable	Three - Discharged Seven -Much Improved
	All - ELISA and Neutralizing Antibodies Increased All - Viral Loads Negative	Five - Neutralizing Antibody Titers Increased Seven - RT-PCR** Became Negative (Three Negative Pretransfusion)
	Four - Procalcitonin, IL-6-Decreased All - CRP – Decreased	Seven - Lymphocytopenia Improved
	Treated 10 to 22 days Postadmission	Treated 16.5 Days (IQR***, 11.0 to 19.3) Postadmission

**Sequential Organ Failure Score*
***Reverse transcriptase-polymerase chain reaction*
****Interquartile range*

Blood Center Role: Blood centers supply all types of blood components to hospitals from healthy volunteer donors. CCP is collected using the same manufacturing process, labeling, and expiration date standards as other apheresis plasma products.[6] Most CCP units will be frozen and stored for one year. CCP is for investigational use only and is labeled with a tag stating: "Caution: New Drug--Limited by Federal (or United States) law to investigational use."[10]

Donor Eligibility:[6] To donate CCP, the donor must have documented evidence of previous COVID-19 diagnosis by a nasal swab at the time of illness OR positive blood test for SARS-CoV-2 antibodies after recovery if prior testing was not performed. Also, the donor must be symptom-free for at least 28 days prior to donation OR at least 14 days prior to donation AND a negative result for COVID-19 by nasal swab or blood test as well as meet all donor eligibility requirements for all blood donors (e.g. feeling well and healthy, age, weight, etc.).[11]

Frequency of donation is every 28 days; however, this can be shortened with blood center medical director approval. Donors will be tested for infectious diseases and ABO and Rh type.[6] An extra lab tube may be collected to analyze antibody levels of donors at a later time if testing is not currently available. For TRALI mitigation, females who have ever been pregnant will be tested for HLA antibodies. If the result shows the presence of HLA antibodies, the plasma will not be used for transfusion.

CCP Ordering Process and Distribution: Treating clinicians should contact the hospital blood bank if considering transfusion of CCP for a patient. The ordering hospital may be asked to provide an eIND (FDA Form 3926) or evidence of participation in a clinical trial (Mayo EAP IND or IND) for a specific patient to the blood center. Each hospital must have a protocol for transfusion of CCP. While the hospital blood bank will place order for CCP; distribution is determined by blood centers.

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