Transfusion, COVID-19 Convalescent Plasma (CCP) (Lab Tests and Diagnostic Procedures)

Overview

On December 31, 2019, the World Health Organization (WHO) first became aware of an infectious outbreak in China, which, since that time, has become a global pandemic. At the time of this publication, the viral agent, acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resultant disease, coronavirus disease 2019 (COVID-19), has been implicated in more than 6,300,000 cases and more than 189,000 deaths in the US alone (9/8/20). Since there is currently no natural immunity in the population and no established treatments or effective vaccine, cases continue to increase. Currently physicians and researchers are investigating and implementing a number of possible treatments including passive antibody administration using plasma from recovered patients. The product is known as COVID-19 Convalescent Plasma or CCP.

The administration of passive antibody is not a novel idea. The use of convalescent plasma from recovered patients has been in use as a therapeutic modality for the treatment of infectious disease for more than 100 years. Its use in the treatment of various viral infections (eg, hemorrhagic fevers [Ebola], influenza [H1N1], and other coronavirus infections [SARS-CoV-1 and MERS]) have resulted in varying degrees of clinical efficacy. Few studies to date have had a high degree of scientific rigor making it difficult to draw valid conclusions regarding the effectiveness of passive antibody administration; however, some data suggest that administration of passive antibody may result in decreased severity and lower mortality rates.

On August 23rd, the FDA issued an Emergency Use Authorization (EUA) for the use of COVID-19 Convalescent Plasma for **hospitalized patients with COVID-19**. This authorization was based on early data suggesting that CCP was safe and potentially effective. Providers who administer CCP under the EUA do not have to report its use to the FDA; however, record keeping requirements exit.

Convalescent plasma may also continue to be provided under an expanded access, investigational new drug application (IND) as a single patient IND for emergency use or through clinical trials. Under the new guidelines "**COVID-19 Convalescent Plasma**" (CCP) refers to plasma authorized under the EUA and convalescent plasma that is provided under an IND is called "**investigational COVID-19 convalescent plasma**" (iCCP). The FDA document emphasizes that the EUA does not replace clinical trials and that additional well-controlled clinical trials are necessary to further inform thinking on the use of CCP for COVID-19 patients.

Note: The information that follows refers only to CCP collected and administered under the EUA.

Use/Indications

Antibodies present in convalescent (immune) plasma may have a therapeutic effect through a number of possible mechanisms including:

- Neutralizing antibodies may bind to the virus or other infective agent directly.
- Antibodies may act indirectly through antibody-mediated pathways such as complement activation, phagocytosis and/or antibody-mediated cellular cytotoxicity.

- Non-neutralizing antibodies may bind to virus particles and may enhance the prophylactic effect and improve recovery (Bloch 2020).

Special Instructions

Under EUA

CCP donor requirements:

- Eligible donors include individuals who have had symptoms of COVID-19 **and** a positive result with a diagnostic test for COVID-19 that has been approved, cleared, or authorized by the FDA, **OR** individuals who have not had a positive COVID-19 diagnostic test or symptoms of COVID-19, but who have a positive test for **SARS-CoV-2 antibodies** using **two different tests** approved, cleared or authorized by the FDA.
- Other donor requirements include:
    - Complete resolution of symptoms at least 14 days prior to donation (a negative diagnostic test for COVID-19 is **not** required to qualify).
    - Male donors, females who have never been pregnant, or female donors who have been tested since their last pregnancy and who are negative for HLA antibodies [to reduce the risk for transfusion-related acute lung injury (TRALI)].
    - Must meet all other requirements for standard whole blood collection including testing for infectious disease; additional requirements must be met if plasma is collected by apheresis (21 CFR 630.10 and 21 CFR 630.15).

Collection

Donor components are obtained via whole blood collection or apheresis plasma collection in an FDA registered or licensed blood collection facility. Apheresis is generally recommended in order to optimize the CCP yield. In the EUA pathway, an IND is **not** required to collect, distribute, and administer CCP.

All collections under the EUA must be tested for anti-SARS-CoV-2 antibodies prior to release. Blood centers are required to use Ortho VITROS SARS-CoV-2 IgG. A signal-to-cutoff (S/C) value of 12 or greater is considered a "high titer". Those with positive results below 12 are considered to be "low titer" units (FDA EUA 2020). (If blood processing establishments wish to use other commercial tests for anti-SARS-CoV-2 they should contact the FDA with data to support the acceptability of the proposed test.) (FDA EUA 2020).

CCP must be labeled in accordance with requirements in 21 CFR 606.121. Additional requirements specific to CCP include:

- Since the product is not licensed, no license number should appear on the label
- Based on the test results units must be labeled as "high titer convalescent plasma" or "low titer convalescent plasma"
- The ISBT uniform labeling format is recommended

- The manufacturing process and expiration date should be the same as for other plasma products of the same type (eg, COVID-19 Convalescent Plasma, Fresh Frozen is frozen within 8 hours and stored at -18°C or below for up to one year).

Components include:

- **CCP, Fresh Frozen:** This component is frozen at ≤18°C within 8 hours of collection. It expires 1 year from date of collection. OR
- **CCP, Frozen:** This component is frozen within 24 hours of collection. It is stored at 1°C to 6°C for up to 24 hours and frozen at ≤18°C. It expires 1 year from date of collection.
- **Units must be thawed at 37°C in a suitable thawing device and refrigerated for a maximum of 5 hours prior to administration.**

Limitations

- Difficulty identifying and recruiting donors who have developed detectable neutralizing antibodies during convalescence
- Lack of validated SARS-CoV-2 antibody tests

Test Includes

Recipient ABO type. Additional compatibility testing is not required.

Selection of ABO Compatible Plasma

Patient ABO Type (Recipient)	**Suitable FFP Types (Donor)**
Group O	Group O, A, B, or AB
Group A	Group A or AB
Group B	Group B or AB
Group AB	Group AB

Recipient Requirements

- Recipient informed consent must be obtained and must include a description of risks and benefits, alternative therapies if available, an opportunity to ask questions, and the right to refuse treatment
- Processes must be in place to verify the identity of the recipient and include a clerical check of physician order and unit identification.

Specimen

Blood (from recipient for pretransfusion ABO typing)

Container(s)

- Recipient specimen: Red top (no additive) tube, lavender top (EDTA) tube, or pink top (EDTA) tube; do not use a serum separator tube.

Volume / Minimum Volume

Tube filled to capacity or 7 mL blood / 3 mL minimum

Collection

Collection of ***recipient specimen*** for pretransfusion work-up: Routine venipuncture. As required by *AABB Standards for Blood Banks and Transfusion Services* all patients must be identified by two independent, identifiers. At bedside, patient identity should be confirmed. Specimen(s) should be labeled with the independent identifiers and the date of collection. There must be a process to identify the person who drew the sample. The tube must be labeled **before** the phlebotomist leaves the room. Use a computer generated label, if available, to avoid transcription errors.

Processing and Storage

- Recipient specimen: Specimen(s) may be collected and transported at room temperature. Processing will be performed by the Transfusion Service. Specimen(s) that cannot be processed and tested immediately should be stored at 2°C to 8°C.

Stability

Recipient specimen: Specimen should be tested within a maximum of 14 days of collection. Institutional policies and procedures should be followed.

Administration

- Administration should conform to institutional guidelines for the administration of plasma products including adherence to all recipient identification procedures.
- CCP must be administered through a standard blood component filter (170-260 microns).
- Recommended dosage is one unit of CCP with an additional unit as warranted based on patient response and clinical judgment.
- Administration may be contraindicated in patients with a history of severe reactions to the transfusion of plasma-containing blood products.
- Product-specific EUA fact sheets should be made available to health care providers and patients respectively:
    - Fact Sheet for Health Care Providers
    - Fact Sheet for Patients and Parents/Caregivers
- The patient/caregiver has the right to refuse treatment with CCP.

Aftercare

Recipient Post-transfusion: The recipient must be observed for evidence of adverse reactions during transfusion and for a suitable time period thereafter. A process must be in place for the recognition and reporting of suspected adverse events; institutional policies apply.

If direct monitoring is not possible, as in outpatient settings, the patient and/or caregiver must be given a set of written instructions regarding possible adverse reactions and a mechanism to report any suspected reactions.

Potential Adverse Reactions:

- Potential for antibody dependent enhancement (ADE) in which plasma antibodies enhance viral cell entry and replication resulting in disease exacerbation.
- Passive antibody administration may suppress the recipient's immune system resulting in increased susceptibility to reinfection.
- Other risks associated with plasma transfusion including transfusion-related acute lung injury (TRALI), transfusion-associated dyspnea, transfusion-related circulatory overload (TACO), and severe allergic reactions.
- All adverse reactions must be thoroughly investigated and reported to the FDA. Records of the investigation of adverse reactions must be maintained by the transfusing institution.
- All records related to the administration of CCP must be maintained until notified otherwise by the FDA and in accordance with institutional guidelines and state and local regulations.
- As with all blood products, fatalities related to the administration of CCP must be reported to the FDA (21 CFR 606.170)

Additional Information

A recent systematic review of the literature reported that CCP may reduce mortality in seriously ill patients, result in an increase in antibody titers and reduction in viral RNA, and cause a reduction in clinical symptoms. These observations were based on limited data and large multicenter clinical trials were recommended. (Rajendran 2020).

HHS has declared a limited waiver on HIPAA sanctions in order to facilitate the identification and recruitment of donors who have recovered from COVID-19 (HHS 2020).

Index Terms

CCP; COVID-19 Convalescent Plasma

Applies to

Coronavirus Disease; COVID-19; SARS-CoV-2

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