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

Overview

General Information

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, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resultant disease, coronavirus disease 2019 (COVID-19), has been implicated in more than 400 million cases worldwide and more than 900,000 deaths in the US alone (2/14/2022) (CDC COVID Tracker 2022). Currently health care providers 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.

Guidelines, Recommendations, and Regulations

On August 23, 2020, the **FDA** issued an Emergency Use Authorization (EUA) for the use of COVID-19 Convalescent Plasma (CCP) for hospitalized patients with COVID-19. This authorization was based on early data suggesting that CCP was safe and potentially effective. On February 4th, 2021 the FDA issued updates to the August EUA. These updates, which were based on data from clinical trials, clarified that the authorization is limited to use of only high titer COVID-19 convalescent plasma in hospitalized patients early in the course of disease, and those hospitalized with impaired humoral immunity who cannot produce an adequate immune response. Additional revisions (February 23, 2021 and March 9, 2021) provided revised the lists of tests that were authorized for the manufacture of CCP and acceptable cut-offs for determination of antibody titers used to define "high-titer" CCP. On December 28th, 2021, the FDA reissued the EUA authorization for the use of COVID-19 convalescent plasma in its entirety with **revisions** that both limited and expanded its use. As of this date, **high-titer CCP use is limited to those patients who have immunosuppressive diseases or those receiving immunosuppressive therapy.** However, the language in the revision expands the use of CCP in these categories of patients to include **both inpatient and outpatient settings** (expanded from previous restriction to inpatient use only) (HHS/FDA EUA Dec 2021). The FDA based their current authorization on a review of observational studies and randomized clinical trials (RCTs) and have concluded that the clinical benefits of CCP used in the manner outlined in these recent revisions outweigh the known and potential associated risks.

CCP is not authorized for treatment of COVID-19 in hospitalized **immunocompetent patients**. Data from RCTs do not demonstrate a positive risk/benefit ratio in these individuals (FDA Fact Sheet 2021). Note: CCP remains an investigational product and as such it is **neither approved nor licensed for any indication**.

Accumulated clinical trial data suggest that **low titer CCP** may not be effective in treating COVID-19 and its use is **not authorized under the EUA**.

In December 2021 the **World Health Organization (WHO)** updated recommendations on the use of COVID-19 convalescent plasma (CCP). WHO recommendations were based on a review of 16 randomized clinical trials (RCTs) enrolling 16,236 patients across three severity subgroups: nonsevere,

severe, and critical. WHO recommendations differ from those of the FDA discussed above. The WHO **strongly recommended against the use** of CCP in **nonsevere** COVID-19 patients. In a review of RCTs, CCP was not found to have an impact on mortality (high quality of evidence) or the need for mechanical ventilation (moderate quality of evidence). For **severe and critically-ill** patients the use of CCP is recommended **only in clinical trials**. Data from RCTs reported that CCP had little or no effect on survival, the need for mechanical ventilation, or time to symptom improvement (quality of evidence very low – low due to risks of bias and imprecision). In addition, the use of CCP was associated with issues of feasibility, acceptability, equity, and cost (WHO 2021 living guidelines).

Both agencies strongly recommend the continuation of well-designed clinical research to provide further data regarding the safety and effectiveness of CCP in COVID-19 patients.

Providers who administer CCP under the EUA do not have to report its use to the FDA; however, record keeping requirements exit.

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

Use/Indications

Indicated for immunocompromised COVID-19 patients in either an inpatient or outpatient setting.

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/reactive test for **SARS-CoV-2 antibodies** using **two different tests** approved, cleared or authorized by the FDA.
- Donors 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).
- Other donor requirements include can be found in the AABB Toolkit (1/10/22) and the FDA's Investigational Guidance for Industry (1/7/22)

CCP Donor Deferrals

- **Donation of CCP following CCP Transfusion**
    - CCP donors must meet all allogeneic blood donor criteria and deferral requirements, including the 3-month deferral from the date of CCP transfusion.
- **Donation of CCP following COVID-19 Vaccine (AABB 2021; HHS/FDA 2022):**
    - Individuals who have never been infected with SARS-CoV-2 which causes COVID-19 and have received a COVID-19 vaccine are **NOT** eligible to donate CCP.
    - Individuals who have recovered from COVID-19 (and who are eligible to donate [above]), and have also received a COVID-19 vaccine post recovery are eligible to donate only if they
        1. had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA, **and**
        2. received the COVID-19 vaccine after diagnosis of COVID-19, **and**
        3. are within 6 months after complete resolution of COVID-19 symptoms
- **Recommended CCP donor deferrals following COVID-19 Vaccine based on vaccine type (AABB 2021; HHS/FDA 2022):**
    - A nonreplicating, inactivated or m-RNA-based COVID-19 vaccine – no waiting period prior to donating
    - A live-attenuated viral COVID-19 vaccine or type of vaccine unknown – recommended 14-day deferral prior to donating
- **Recommended CCP donor deferrals following Monoclonal Antibody Therapy (AABB 2021; HHS/FDA 2022):**
    - To ensure that donor antibodies are a direct result of COVID-19 infection, it is recommended that donors be deferred for at least three months following receipt of:
        - Investigational COVID-19 monoclonal antibody therapy as part of a clinical trial, **or**
        - Authorized/licensed COVID-19 monoclonal antibody therapy

Note: The blood establishment's medical director has final responsibility for the evaluation of prospective donors and determine eligibility (21 CFR 630.10).

Collection of CCP

- 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 as it optimizes CCP yield; RBCs are returned to donor during apheresis process, thus no transient anemia; and donors can donate more frequently.

- All collections under the EUA must be tested for anti-SARS-CoV-2 antibodies prior to release. See FDA EUA update December, 2021 for a table listing the acceptable assays and corresponding cutoff values (HHS/FDA EUA 2021).
- CCP must be labeled in accordance with requirements in 21 CFR 606.121, including a "high titer convalescent plasma" label.

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 of CCP

- Difficulty identifying and recruiting donors who have developed detectable neutralizing antibodies during convalescence
- Lack of empirical studies demonstrating effectiveness

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), a theoretical risk, 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-transmitted infection, 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)

Laboratory/Diagnostic Pearls

- Current data suggest that CCP may be less effective against some variant strains, although it is not a reason to avoid use (Wibmer 2021; Cele 2021).
- In contrast to hyperimmune globulins and monoclonal antibodies, CCP cannot be concentrated to raise the antibody titer.
- As of December 2021, over 250,000 units of CCP have been administered in the US through the expanded access program, EUA or within a clinical trial.

Additional Information

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.

The National Institute of Health (NIH) and Infectious Diseases Society of America (IDSA) both concur that more studies/trials are necessary to determine whether there is actual benefit from treatment with convalescent plasma for COVID-19 patients. Current data suggests CCP is most useful when given early in disease course and with a high neutralizing antibody titer (IDSA 2022; NIH 2021). But both organizations have recently released statements recommending against the use of CCP for most patients (IDSA 2022; NIH 2021). To date, the majority of clinical trials have not provided evidence supporting the use of CCP in nonsevere or severe hospitalized patients with COVID-19. However, a number of study design issues need to be addressed (Korley 2021). Lack of efficacy may have been related to patient selection, effect size, insufficient doses or titers of antibodies, age of the patients, assays used to select CCP donors, variations across viral genotypes, effectiveness if administered prior to the development of native antibodies, or the impact of the use of CCP with concurrent administration of other therapeutics (Korley, 2021).

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.

US Department of Health and Human Services (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; COVID-19 Treatment; SARS-CoV-2

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