Introduction

The U.S. Food and Drug Administration (FDA), a key participant in the exploration of potential therapies to fight the SARS-CoV-2 (COVID-19, the novel Coronavirus) pandemic, has investigated the use of COVID-19 convalescent plasma (CCP), an unapproved biological product containing antibodies collected from recovered individuals who previously tested positive for COVID-19. Preliminary data from the clinical trials has proven promising, but limited. Therefore, the FDA has not yet approved COVID-19 convalescent plasma for any indication and will continue to evaluate the use of CCP on an ongoing basis as additional data becomes available.

Prior to 8/23/2020, convalescent plasma was administered only by organizations that had enrolled in clinical trials, most notably through the Mayo Clinic Expanded Access Protocol (EAP) or through a single patient emergency IND (eIND) application. On 8/23/2020, the FDA issued an Emergency Use Authorization (EUA) for administration of CCP to any hospitalized COVID-19 patient who meets the criteria to receive the product, even if the organization had not previously enrolled in a clinical trial (the Mayo Clinic EAP ended as of 8/31/2020).

Plasma donations must be tested, per the EUA, using the Ortho VITROS SARS-CoV-2 IgG test for antibodies to determine suitability before release. To enable use of the current inventory and to ensure uninterrupted access to CCP for hospitalized patients, the FDA anticipates a transition of two to three months (potentially November, 2020) will be required for blood centers to implement the requisite antibody titer testing and the new high and low titer product labeling per the EUA guidance. In the interim, and as permitted by the FDA, the Red Cross will continue to distribute convalescent plasma labeled for investigational use. This product is not labeled with a titer but will have met all other eligibility criteria described in the EUA guidance.

Importantly, any provider who wishes to administer CCP must review the documents contained in this toolkit and follow the instructions as outlined (In particular, see https://www.trinity-health.org/covid-19-resources/_assets/documents/clinical-guidance/treatment/convalescent-plasma-transition-plan-under-the-emergency-use-authorization.pdf

Use of Convalescent Plasma

CCP, as with all blood products, is limited in supply and is an option for patients with severe disease. Consider performing a risk-benefit assessment of the patient prior to prescribing to conserve resources.

COVID-19 Convalescent Plasma (CCP) Emergency Use Authorization (EUA) Summary

Overview

- The full CCP Emergency Use Authorization can be found on the FDA website at https://www.fda.gov/media/141477/download
- COVID-19 Convalescent Plasma (CCP) should not be considered a new standard of care for the treatment of patients with COVID-19.
- It is used for the treatment of hospitalized patients with COVID-19 when administered as described in the Scope of Authorization.

Testing

- Donations: Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable for Convalescent Plasma donation (21 CFR 630.30).
  - Plasma donations must be tested by registered or licensed blood establishments for anti-SARS-CoV-2 antibodies as a manufacturing step to determine suitability before release.
  - Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) value of 12 or greater qualify as high titer COVID-19 convalescent plasma.
    ▪ If a blood establishment is considering using an alternative test in manufacturing in order to qualify high titer COVID-19 convalescent plasma, they should contact the FDA Center for Biologics Evaluation and Research (CBER) to determine acceptability of the proposed test, which if accepted, would require an amendment to this EUA
- Tested Units and Labeling:
  - Units containing anti-SARS-CoV-2 antibodies but not qualified as high titer by the test described above are considered low titer units and must be labeled accordingly.
    ▪ The health care provider may assess whether units with a S/C value of less than 12 (labeled as low titer) are acceptable for use based on an individualized assessment of benefit-risk.

Dosage

- Clinical dosing may first consider starting with one COVID-19 convalescent plasma unit (about 200 mL), with administration of additional COVID-19 convalescent plasma units based on the prescribing physician’s medical judgment and the patient's clinical response.

Disclosures

- COVID-19 convalescent plasma is authorized to be accompanied by the following product-specific information pertaining to emergency use, which is required to be made available to health care providers and patients respectively:
    ▪ Changes to the authorized Fact Sheets may be requested by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR)
Blood Bank Requirements

A. Registered or licensed blood establishments will ensure that the authorized COVID-19 convalescent plasma, accompanied with the authorized labeling (i.e., Fact Sheets), is distributed to hospitals consistent with the terms of this letter, and that such hospitals are aware of the letter of authorization.

B. Registered or licensed blood establishments will ensure that appropriate storage and cold chain is maintained. The authorized COVID-19 convalescent plasma should be frozen after collection and stored at -18°C or colder. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

C. Through a process of inventory control, registered or licensed blood establishments will maintain records regarding distribution of the authorized COVID-19 convalescent plasma (i.e., donor records, quantity, receiving site, receipt date).

D. Registered or licensed blood establishments will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals Requirements

A. Hospitals and health care providers receiving authorized COVID-19 convalescent plasma will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to health care providers and to patients and caregivers, respectively, through appropriate means.

B. The authorized COVID-19 convalescent plasma must be stored frozen at -18°C or colder. Once thawed and refrigerated, the authorized COVID-19 convalescent plasma must be used within 5 days for patient transfusion.

C. Hospitals and health care providers administering COVID-19 convalescent plasma will track serious adverse events that are considered to be potentially attributable to COVID-19 convalescent plasma use and must report these to FDA in accordance with the Fact Sheet for Health Care Providers. Health care providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required under 21 CFR 606.170.

D. Through a process of inventory control, hospitals will maintain records regarding the administered authorized COVID-19 convalescent plasma (e.g., donation identification number, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

E. Hospitals will ensure that any records associated with this EUA are maintained until notified by ASPR and/or FDA. Such records will be made available to ASPR, HHS, and FDA for inspection upon request.

Printed Matter, Advertising, and Promotion

All descriptive printed matter, including advertising and promotional material, relating to the use of COVID-19 convalescent plasma clearly and conspicuously shall state that:

- COVID-19 convalescent plasma has not been approved or licensed by FDA;
- COVID-19 convalescent plasma has been authorized by FDA under an EUA;
- COVID-19 convalescent plasma is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

**Transition to the Emergency Use Authorization (EUA)**

On Aug. 28, 2020, the American Red Cross provided transitional guidance through a blast email to sites that previously participated in convalescent plasma clinical trials:

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Dear Transfusion Medicine Partner,

After further clarification from the FDA, I want to provide you with an update on the Emergency Use Authorization (EUA) for the use of COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. To enable use of current inventory and to ensure uninterrupted access to CCP for hospitalized patients, the FDA anticipates a transition of two to three months will be required for blood centers to implement the requisite antibody titer testing and the new high and low titer product labeling per the EUA guidance. In the interim, and allowed by FDA, the Red Cross will continue to distribute convalescent plasma labeled for investigational use. This product is not labeled with a titer but will have met all other eligibility criteria described in the EUA guidance.

The Mayo Clinic EAP will discontinue enrollment as of this evening, August 28th. Hospitals will no longer be required to have an IND in order to use convalescent plasma. However, hospitals must consent their patients to receive a unit of non-titered plasma. The FDA indicated they will be providing additional guidance on informed consent for hospitals in the coming days. Also, while pediatric patients are not specifically covered in the EUA, FDA is allowing its use for hospitalized pediatric patients to gain access to CCP. As additional information from the FDA and the associated Red Cross implementation timeline becomes available, I will send further updates to your hospital.

To meet your patient needs, you should continue to order CCP, just as before, through Connect. Red Cross will label and distribute investigational use CCP free of charge to hospitals.

I appreciate your support in raising awareness of the ongoing need for COVID-19 donors. The Red Cross has experienced an improvement in our supplies, however I encourage you to continue to direct fully recovered patients and community members to sign up to donate convalescent plasma by visiting RedCrossBlood.org/plasma4covid.

The Red Cross is committed to supporting your hospital during the COVID-19 pandemic including the continued provision of convalescent plasma.

Thank you,
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If your site participated in CCP clinical trials, please see the Convalescent Plasma Transition Plan under the EUA - Interim Guidance for more information about transition to the new EUA.

Order Process - Under Construction

Administration:

- Utilize organizational policy for administration of blood products.
- An order for convalescent plasma is required.
- The patient should be consented for convalescent plasma administration and provided the Fact Sheet for Patients and Parents/Caregivers: Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for Treatment of COVID-19 in Hospitalized Patients.


Adverse Reactions Reporting

See COVID-19 Convalescent Plasma (CCP) Emergency Use Authorization (EUA) Summary above, which addresses the Hospital Requirements (C) for adverse effects reporting (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/CFRSearch.cfm?fr=606.170)
Documentation Requirements

Providers

Health care providers should read the Fact Sheet for Healthcare Providers developed by the FDA prior to ordering COVID-19 Convalescent Plasma. This document is available on the Trinity Health COVID-19 Pulse website for download at: Fact Sheet for Healthcare Providers

Prior to CCP administration, patients or caregivers should be given the Fact Sheet for Patients and Caregivers and must consent to treatment with COVID-19 Convalescent Plasma. Until blood providers are fully compliant with the EUA (including testing and titer level labeling), providers must give the patient or caregiver a modified Fact Sheet that outlines that the convalescent plasma they will be given does not fully meet all the requirements of the EUA and was manufactured under the standards of the previous Emergency Access Program. The modified document is available on the Trinity Health COVID-19 Pulse website for download: Fact Sheet for Patient and Parents/Caregivers (Interim)

Once blood providers are fully compliant with the testing and titer labeling requirements as outlined in the EUA, the EUA Fact Sheets can be downloaded from the FDA website at: Fact Sheet for Patient and Parents/Caregivers

- The patient or parent/caregiver must sign a consent to receive COVID-19 Convalescent Plasma (CCP). Until a specific CCP consent form is developed, follow the guidance in the Convalescent Plasma Transition Plan under the EUA - Interim Guidance.

Provider documentation should reflect that the patient has been provided with and accepts the disclosures as outlined in the Fact Sheet for Patients and Caregivers.