

Points to consider in the preparation and transfusion of COVID-19 convalescent plasma

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Important notices:

- Because the safety and efficacy of convalescent COVID-19 plasma as a treatment for COVID-19 are unproven at this time, clinical use of this product should be managed as an experimental therapy consistent with ethical and legal safeguards (informed consent of donors and patients, institutional approval, special labeling as an investigational product, compliance with applicable regulatory requirements).
- Ideally, COVID-19 plasma should be used in the context of an organized research study designed to determine its safety and efficacy in comparison with standard of care or other therapeutic interventions. Even if used empirically it is vital to ensure monitoring of patient outcomes including clinical and laboratory indicators of safety and efficacy to maximize the knowledge that might be gained.
- Collection and retention of blood specimens from both donors and recipients (pre- and post- treatment) should be performed to permit retrospective determination of the characteristics of an effective product and dosage regimen, and the characteristics of patients most likely to benefit.
- General information on the rationale and approach to use of convalescent plasma in virus epidemics can be found in the “WHO Blood Regulators Network (2017) Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus.” (1)

Intentional collection of convalescent plasma **should be performed only by apheresis in order to avoid unnecessary red cell loss in the donor and to optimize the volume of plasma that can be generated for investigational use.** In instances of routine whole blood donation by a previously infected person who meets current suitability criteria, COVID-19 convalescent plasma can be prepared by component separation and considered for investigational use if not critically needed for general patient care. Transfusion of whole blood to provide convalescent plasma should be avoided unless use of whole blood is clinically indicated.

Key Points:

- A. Eligibility of convalescent COVID-19 patients to donate whole blood or plasma should be based on:
 - a. Confirmation of previous infection with SARS-CoV-2 by a record of a validated diagnostic test at the time of illness
 - b. **An interval of at least 14 days after full recovery.**

- c. Standard selection criteria for whole blood or plasma donation according to local requirements and standards (age, weight, collection frequency, vital signs, freedom from deferral criteria) in line with “WHO Blood Regulators Network (BRN): Donor selection in case of pandemic situations” (2)
- d. Non-reactivity of blood samples for transfusion transmitted infections including HIV, HBV, HCV, syphilis (for whole blood) and locally transmitted infections using approved serological and/or nucleic acid tests, consistent with local requirements for collection of blood components for transfusion.
- e. To avoid the risk of Transfusion Related Acute Lung Injury (TRALI) preference should be given to use of plasma from male donors or from female donors who have never been pregnant including abortions. This measure lowers the possibility of presence in the plasma of the antibodies to HLA or granulocyte antigens that cause TRALI. TRALI occurs within 6 hours after transfusion of implicated plasma and can be severe. (3)

B. Pre-screening and pre-donation testing of convalescent COVID-19 donors

- a. Recovery from COVID-19 infection should be confirmed through:
 - 1. Physical examination of the donor to establish good health including absence of fever and respiratory symptoms
 - 2. If plasma is collected prior to 28 days after full recovery from illness, then confirmation of the resolution of the infection should be obtained through demonstration of two non-reactive Nucleic Acid Tests (NAT) for SARS-CoV-2 performed at an interval of at least 24 hours on nasopharyngeal swabs
 - 3. Viral inactivation of convalescent plasma is encouraged to address residual risks of known transfusion transmissible viruses in an experimental product.
 - 4. The approximate date of COVID-19 infection, history of symptoms, treatments received and date of resolution of all symptoms documented and traceable
 - 5. When feasible, the total and neutralizing titers of anti-SARS-CoV-2 antibodies should be determined as part of product characterization before use. Furthermore, donor blood/serum/plasma samples should be saved frozen at -80°C for retrospective testing and further scientific investigations.

C. Criteria for collection of COVID-19 plasma

- a. Performed in certified blood establishments (or under exceptional circumstances hospitals and other health care facilities routinely engaged in performing whole blood collection with plasma separation and/or apheresis procedures) by appropriately trained staff
- b. Use only of legally approved blood collection or plasmapheresis equipment under standard operating procedures
- c. Supervision of the collection process by trained staff

- d. Volume of plasma to be collected: at least 200 to 600 mL (without anticoagulant) based on the procedure and regulatory limits
- e. Plasma units intended for use as convalescent plasma should be clearly labeled.¹
- f. The first plasma donation can be followed by further donations at a frequency compliant with local regulations and taking into full account the health status of the donor (in many jurisdictions the interval between apheresis plasma donations of 600 mL or more should not be less than 7 days and that between whole blood donations should be at least eight weeks).

D. Post-donation treatment of plasma:

- a. Where feasible, pathogen inactivation of plasma using a licensed technology is highly desirable to control residual risks of transfusion transmitted infectious diseases and to allay concern about possible superinfections with SARS-CoV-2.
- b. Freezing as soon as possible at -20°C or preferably colder and stored frozen until administration
- c. Convalescent plasma collected from donors who do not fulfill post-COVID-19 suitability criteria for blood donation should be stored separately from other blood products in inventory
- d. Plasma samples aliquots should be taken for archiving at -80°C and future potential scientific investigations

E. Recommendations for plasma transfusion:

- a. Follow standard hospital procedures and recommendations for thawing and transfusion of plasma
- b. It is crucial to ensure ABO compatibility between the donor and the recipient
- c. Transfusion of plasma from at least two donors may be therapeutically beneficial to achieve more effective immune protection from delivery of diverse antibodies.
- d. In the absence of published peer-reviewed reports of transfusion of convalescent COVID-19 plasma, patients could receive an initial dose of 200 mL, followed by one or two additional doses of 200 mL according to disease severity and tolerance of the infusions.
- e. Blood/serum/plasma samples of the recipient prior to and after transfusion should be taken for future potential scientific investigations.

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Disclaimer: Jay Epstein's contributions to this article reflect his own views and should not be construed to represent FDA's views or policies.

References:

¹ ISBT128 product description codes for convalescent plasma are available for establishments using the ISBT128 information standard

1. WHO Blood Regulators Network (2017) Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus
[https://www.who.int/bloodproducts/brn/2017 BRN PositionPaper ConvalescentPlasma.pdf?ua=1](https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1)
2. WHO Blood Regulators Network (BRN): Donor selection in case of pandemic situations
<https://www.who.int/bloodproducts/brn/DonorSelectionincaseofPandemicSituations.pdf?ua=1>
3. P. Toy. Update on Transfusion-Related Acute Lung Injury. *Clinical Advances in Hematology & Oncology*: 2019; 17(7): 378-381.