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Special Report

Points to consider in the preparation and transfusion of COVID-19 convalescent plasma in low– and middle–income countries

Smid WM [1](chair), Burnouf T[2], Epstein J[3], Kamel H[4], Sibinga CS[5], Somuah D[6], Stramer SL[7], and Wendel S[8]

[1] Sanquin Consulting Services, Academic Institute IDTM, Amsterdam, the Netherlands

[2] College of Biomedical Engineering, Taipei Medical University, Taipei, Taiwan

[3] US Food and Drug Administration, Silver Spring, MD, USA

[4] Vitalant, Scottdale, Arizona, USA

[5] IQM Consulting, Zuidhorn, The Netherlands

[6] Anglogold Ashanti Health Foundation Hospital, Obuasi, Ghana

[7] American Red Cross, Washington, MD, USA

[8] Blood Bank, Hospital Sirio Libanês, São Paulo, Brasil

Corresponding Author:
Smid WM
M.Smid@sanquin.nl

Conflict of Interest:
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Preamble:

- Although early reports have been promising[1,2], the safety and efficacy of COVID-19 convalescent plasma as a treatment for COVID-19 are unproven at this time. However, absent any known effective therapy, the theoretical benefit and feasibility of local production of COVID-19 convalescent plasma have generated global priority for its investigational use.
- Enabling the availability of quality and safe COVID-19 convalescent plasma in low- and middle- income countries (LMIC) requires specific attention to resource limitations that may affect donor selection, product characterisation and clinical use in addition to assuring adherence to good manufacturing practices for blood establishments.[3] LMIC also may lack an organised and nationally regulated blood system with the capacity to manage a national initiative to provide COVID-19 convalescent plasma.
- The Working Party on Global Blood Safety of the International Society of Blood Transfusion has published "Points to Consider in the preparation and transfusion of COVID-19 convalescent plasma" that are recommended as best current practices to be followed whenever feasible including in LMIC.[4]
- WHO Blood Regulators Network (BRN) Position Paper on use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus can also serve as guidance on general aspects pertaining to the collection of convalescent blood and plasma.[5]
- The technological and manpower infrastructure in many LMIC is limited constraining capabilities for blood collection, donor and donation testing, separation of whole blood into components, and product storage. Strategies to provide COVID-19 convalescent plasma must rely on the collection and testing procedures in use locally and must avoid aggravating blood shortages that may result from disruptions during the pandemic.
- The collection and clinical use of convalescent COVID-19 plasma should be done under the responsibility of National Blood Services and the supervision of Ministries of Health to assure legal and ethical use of an investigational therapy.
- Whenever feasible COVID-19 convalescent plasma should be provided in the context of an organised randomised/controlled clinical trial or a protocol-driven observational study. Where this is not possible, efforts nevertheless should be made to obtain and archive blood samples from donors and recipients for future scientific study and to document patient outcomes.

- The protection of donor and recipient remains key priorities. The best possible practices in place in the country for the collection of blood or plasma should be followed to perform the collection of convalescent blood or plasma, and to protect both the donor and the recipient, in compliance with applicable regulatory requirements. COVID-19 convalescent plasma should be obtained only from volunteer, non-remunerated donations.
- As the use of aphaeresis for plasma collection is uncommon in many LMIC, collection of convalescent whole blood will often be the only possible option. Measures should be taken to avoid unnecessary red cell loss and compromising haemoglobin level in the donor donating whole blood, while optimising the volume of recovered plasma generated through component separation.
- Transfusion of convalescent whole blood could be considered only if the 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 clinical records that document a medical diagnosis of COVID-19 by signs and symptoms of the illness and, where feasible, a positive Nucleic Acid Test (NAT) for SARS-CoV-2.
b. An interval of at least 28 days after full recovery except as provided in B.a.3.
c. Standard selection criteria for blood donation according to local requirements and standards (age, weight, collection frequency, vital signs, freedom from deferral criteria).
d. ABO and RhD testing to ensure blood group compatibility with a possible recipient.
e. Haemoglobin measurement or validated haemoglobin estimation.
f. Non-reactivity of blood samples for transfusion transmitted infections including HIV, HBV, HCV, Syphilis and locally transmitted infections, such as malaria and Chagas disease, using in vitro diagnostic systems locally licensed for the testing of blood components for transfusion.
g. Blood collection should be done from male donors or from female donors who have never been pregnant including miscarriages and abortions, or taking into consideration current local practices in the transfusion of plasma. This measure lowers the possibility of presence in the plasma of the antibodies to HLA or granulocyte antigens that cause Transfusion Related Acute Lung Injury (TRALI). Testing for these antibodies in female donors and in male donors with history of transfusion is desirable as an added precaution where feasible.

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. The approximate date of COVID-19 infection, history of symptoms, treatments received and date of resolution of all symptoms documented and traceable.
    3. When blood or plasma needs to be collected prior to 28 days after full recovery from illness, the collection should not take place prior to 14 days after full recovery and additional confirmation of the resolution of the infection should be obtained through demonstration of a non-reactive Nucleic Acid Test (NAT) for SARS-CoV-2 performed on a nasopharyngeal swab sample.
    4. Whenever feasible, the donor's plasma should be tested for neutralising titres of anti-SARS-CoV-2 antibodies. Current data suggest that donations with a minimal titre by end-point dilution of 1:80 or preferably 1:160 should be selected. However, further studies are needed to define the minimal titre recommended. Absent a test for neutralising antibodies, and where feasible, donations also can be selected based on high reactivity in a serologic assay for anti-SARS-CoV-2 antibodies.

C. Criteria for collection of COVID-19 blood or plasma

a. Performed in certified blood establishments of the National Blood Services
b. Use only of legally approved blood or plasma collection devices and equipment
c. Supervision of the collection process by trained staff of the National Blood Services
d. Volume of whole blood to be collected: 200-450 mL (plus the anticoagulant/preservative) based on the procedure and regulatory limits; in the case of aphaeresis plasma: 600 mL (plus the anticoagulant)
e. Blood should be separated into the plasma component using standard operating procedures
f. Blood or plasma units intended for use as convalescent products should be clearly labeled.

g. The first blood or 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 including a normal plasma protein level if plasma is collected more than once in 28 days.

D. Post-donation treatment of blood or plasma:

a. Where feasible, pathogen inactivation of plasma using a licensed technology in place in the blood establishment, is desirable to control residual risks of transfusion transmitted infectious diseases and to allay concern about possible superinfections with SARS-CoV-2.
b. Whole blood should be stored between 2°C and 6°C for a duration depending upon the anticoagulant and preservative used.
c. Liquid plasma may be stored between 1°C and 6°C for up to 40 days.
d. Plasma frozen at -18°C or colder within 24 hours after blood collection can be stored for up to 12 months.
e. Convalescent plasma collected from donors who do not fulfill post-COVID-19 suitability criteria for routine blood donation should be stored separately from other blood products in inventory.
f. Convalescent plasma should bear special labeling as an investigational product for treatment of COVID-19.
g. Donor blood/serum/plasma samples obtained at the time of donation should be saved frozen at -20°C or colder for retrospective testing of the total and neutralising titres of anti-SARS-CoV-2 antibodies and further 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 of plasma between the donor and the recipient and avoidance of RhD sensitisation in cases where whole blood is transfused.
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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