



**COVID-19 (nCorona) Virus Outbreak Control and Prevention State Cell
Health & Family Welfare Department
Government of Kerala**

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**COVID-19 – GUIDELINES
PROTOCOL FOR COMPASSIONATE USE OF CONVALESCENT PLASMA FOR
TREATMENT OF PATIENTS WITH SEVERE/CRITICAL COVID-19 INFECTION IN
KERALA**

The World Health organisation has declared COVID-19 as a pandemic. Kerala has been taking all measures to contain the epidemic.

In order to provide all available care and support to ensure the recovery of patient the following guidelines regarding use of convalescent plasma for the treatment on compassionate ground are issued.

1. Convalescent Plasma in COVID-19

Currently, there are no approved treatments for COVID-19. The management plan is supportive care with supplemental oxygen and mechanical ventilation. Multiple trials are being done across the globe to assess the efficacy of various treatment strategies. WHO initiated the SOLIDARITY trial in several countries to compare the effectiveness of the following regimens against COVID-19: Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir with interferon beta, and hydroxychloroquine. US FDA has approved Convalescent Plasma from patients recovered from COVID 19 for the treatment of severe or life threatening COVID-19 infections.

In a small case series, five critically ill COVID-19 patients with ARDS were treated with convalescent plasma containing neutralizing antibodies. Infusion of plasma was followed by improvement in clinical status in all five patients, with no deaths and the study reported that three patients were discharged, whilst two continued to be stable on mechanical ventilation. In another small case series of four patients, including one pregnant woman, it was seen that all four recovered eventually.

In another feasibility study of convalescent plasma therapy, 10 severely ill patients were transfused with 200 ml of convalescent plasma. It was well tolerated with significant increase in neutralizing antibodies and disappearance of viremia in 7 days. Clinical symptoms rapidly improved in 3 days.

Historically, it has been used in viral diseases such as poliomyelitis, measles, mumps and influenza before vaccines became available. A meta-analysis of 1703 patients with H1N1 influenza during the Spanish Flu of 1918 suggested that patients who received convalescent plasma had lower mortality. Conversely, in a double blind, randomized, placebo-controlled trial, convalescent plasma was not found to be superior to placebo in patients infected with Influenza A. Furthermore, 84 patients with Ebola virus disease who were transfused with convalescent plasma without known levels of neutralizing antibodies did not have a survival benefit. Convalescent plasma was also studied during the previous coronavirus outbreak of SARS in 2002 -2004. In a retrospective study of 80 patients by Cheng et al, it was observed that patients who received convalescent plasma before day 14 of illness had better outcomes, defined as early hospital discharge, compared to patients who received after day 14 of illness (15.6% vs 58.3%; $P < 0.001$). Considering the lack of efficacious treatments for COVID 19 and the epidemic situation with high mortality rate, US FDA has approved convalescent plasma for COVID-19 for clinical trials, expanded access and single patient emergency investigational new drugs . Majority of the adverse effects associated with plasma transfusion are non-lethal; medically treatable adverse effects commonly associated with transfusion of plasma include TRALI; transfusion associated circulatory overload (TACO); allergic/anaphylactic reactions; transfusion related transmission of infections (TTI); febrile non-hemolytic transfusion reactions (FNHTR); hemolytic transfusion reactions (HTR); and rarely RBC allo-immunization.

2.Compassionate use of convalescent plasma may be considered in

1. Age \geq 18yrs
2. Laboratory confirmed diagnosis of infection with SARS CoV- 2
3. Severe or life threatening COVID 19
4. Informed consent provided by the patient or relative.
5. Emergency approval from Institutional Human ethics committee.

Severe COVID 19 is defined by one or more of the following

- Respiratory rate \geq 30/min
- Blood oxygen saturation \leq 93% on room air.

- Ratio of Partial pressure of arterial oxygen to fraction of inspired oxygen ratio > 300
- Lung infiltrates > 50% within 24-48 hours

Life threatening COVID 19 infection is defined as one or more of the following

- Respiratory failure
- Septic shock
- Multi organ dysfunction or failure

3. EXCLUSION CRITERIA

1. Age < 18 yrs
2. Known hypersensitivity to blood products.

4. Convalescent plasma:

Eligibility of Donor

The following criteria should be met for potential donors

- ≥ 18 years of age
- Males or female donors of weight >55Kg
- Prior diagnosis of COVID-19 documented by a laboratory test (RT-PCR) with symptomatic disease with at least fever and cough and
- Complete resolution of symptoms at least 28 days prior to donation

or

Complete resolution of symptoms at least 14 days prior to donation and two negative real time PCR test for COVID-19 from nasopharyngeal swab, collected 24 hours apart.

In addition, donor eligibility criteria for whole blood donation will be followed in accordance to the Drugs & Cosmetics Act 1940 and rules 1945 therein (as amended till March 2020).

5. Screening of eligible donor

1. Donor will be screened, followed by brief physical examination.
2. Donors not fit to donate blood based on the history and physical examination will be deferred and excluded from plasma donor pool for a time period specified by country regulation.
3. Donors who have had transfusion of blood products in last 8 weeks will be excluded.
4. Donors who have had COVID diagnosis more than 4 months will be excluded from donation.

5. Two EDTA samples (5 ml each) and one plain sample (5 ml) will be drawn for the following pre-donation tests as required for convalescent plasmapheresis.
 - a. Blood group (ABO grouping and Rh phenotyping) .
 - b. Complete blood count including Hb, Hct, Platelet count, Total and differential leucocyte count. Donors with Hb>12.5g/dl, platelet count >1,50,000 per microliter of blood and TLC within normal limits will be accepted.
 - c. Screening for HIV, HBV and HCV by serology or NAT. Donor negative by either test will be included.
- d. Screening for syphilis and malaria by serology. Negative donors will be included.
 - e. Total serum protein. Donors with total serum protein > 6gm/dl will be accepted (as per Drugs and Cosmetics (Second Amendment) Rules, 2020)
6. Titration of anti-COVID-19 (both IgG and IgM) antibodies and SARS-CoV-2 neutralizing antibodies may be done depending on availability of facilities at the time of testing. Desired titers for IgG antibodies is 1:1024 and for neutralizing antibodies is 1:40. If not done at the time of plasma collection the donor samples will be stored in aliquots at <-80° C to be tested later.

6.Plasmapheresis of donors

Donors will be explained the procedure of plasma donation and the adverse events associated with the process.

Plasma collection will be done by centrifugal separation using any of the apheresis equipment available at the facility. Volume collected will not exceed 500 ml per sitting (as per Drugs and Cosmetics (Second Amendment) Rules, 2020). Throughout the procedure the extracorporeal volume of blood will never exceed >15% of the total blood volume of the donor. Donor adverse events will be managed as per departmental SOP for Apheresis donations.

A donor details will be collected and plasma will be stored or issued for patient use. The collected plasma will be divided into smaller packs of 200 ml each for easy storage and transfusion and frozen within 8 hours. The plasma will be stored at <-40 degree Celsius.

No pooling of plasma from different donors will be done.

Successful plasma donors will be requested to repeat the donation. If the donor agrees for a repeat donation, such donation will be scheduled after at least 2 weeks of the first plasma donation. If there was a loss of red cells at the time of first donation owing to any procedural problems or otherwise,

the donor will be deferred for a period of 3 or 4 months for male or female donors, respectively. All the donor selection guidelines described above will apply to repeat donation as well.

In repeated plasmapheresis:

1. Total serum protein will be tested before the third procedure if done within four weeks and it should be 6 gm/dl.
2. The quantity of plasma separated from the blood of donor will not exceed 500 ml per sitting and once in a fortnight or shall not exceed 1000 ml per month.

7. Infusion of Blood Products

For infusion of plasma, standard SOP for transfusion of FFP should be followed with special care to monitor these patients during and post-24 hours of transfusion. All such transfusions must be done using blood transfusion sets. The clinician will send a request for plasma component specifically mentioning the diagnosis and that convalescent plasma is required. An ABO compatible plasma bag of approx. 200mL will be issued maintaining all the blood bank records after thawing at 37 degree Celsius.

8. Dose of convalescent plasma: The first plasma transfusion of 200ml will be followed by one additional dose of 200 mL at 24 hours interval unless contraindicated. Hence, the cumulative dose of convalescent plasma for each patient will be 400mL. The second plasma unit will preferably be from a different donor depending on the availability of another ABO compatible plasma unit or else plasma unit from the same donor will be issued. (Jay Epstein & Thierry Burnouf, on behalf of the ISBT Working Party on Global Blood Safety. Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. 2020).

9. Expected adverse events (AE)

- Donor-related adverse events: They are divided into local reactions and systemic reactions. AEs were classified according to severity into mild, moderate, and severe and according to etiology in a donor into hypotensive reactions, citrate reactions, hematomas, loss of consciousness, seizures, and allergy.
- Kit/ Equipment-related adverse events: These are secondary to improper disposable sets. These are hemolysis, thrombus formation, air embolism, leakage, infection, improper mounting of the kits etc.
- Recipient related adverse events: A transfusion-related adverse reaction is a response or effect in a patient temporally associated with the administration of blood or blood components. Majority of these are non-lethal and medically treatable. Adverse effects commonly associated with transfusion of plasma

include transfusion related acute lung injury (TRALI); transfusion associated circulatory overload (TACO); allergic/anaphylactic reactions; transfusion related transmission of infections (TTI); febrile non-hemolytic transfusion reactions (FNHTR); hemolytic transfusion reactions (HTR); and rarely RBC allo-immunization.

10. Management of Adverse Events:

1. TRALI – Discontinue transfusion. Notify the blood bank. Treatment is supportive care with respiratory support either with Non-Invasive or Invasive Mechanical Ventilation depending on the clinical scenario.
2. TACO – Stop the transfusion. Notify the blood bank. Respiratory support with supplementary O₂ and assisted ventilation. Fluid mobilization, typically done with diuretics along with careful monitoring of renal function and electrolytes
3. Allergic reactions – Discontinue transfusion. Notify the blood bank. Observe for resolution. Give diphenhydramine 25-50mg orally. Can continue with rest of the transfusion depending on the clinical scenario.
4. Anaphylactic reactions – Discontinue transfusion. Notify the blood bank. The management includes epinephrine 0.3mL of a 1:1000 solution IM. Resuscitation with fluids, O₂, vasopressors.
5. FNHTR – Discontinue transfusion. Notify the blood bank. Administer paracetamol. Evaluate for other causes of fever.
6. HTR – Discontinue transfusion. Notify the blood bank. Diagnosis should be confirmed quickly repeat ABO and Rh compatibility testing. Along with that, vitals should be monitored every 15 min. Aggressive hydration of the patient. If needed vasopressors should be initiated to maintain stable vital signs. Along with this electrolytes, Hemoglobin and cardiac rhythm should be monitored



Principal Secretary

Annexure 1.

SOP FOR CONVALESCENT PLASMA THERAPY IN SEVERE/CRITICAL COVID -19



Annexure 2: INFORMED CONSENT FORM FOR COMPASSIONATE USE OF CONVALESCENT PLASMA FOR SEVERE/CRITICALLY ILL COVID-19 PATIENTS

Institutional Medical board has informed me that I /my relative have been diagnosed with severe/critical COVID-19 infection. They have clearly explained to me that there is no effective and approved medication against COVID-19 infection. They have informed me/relative that severe/critical COVID-19 infection diagnosed in the patient is not responding to the standard treatment administered as per state treatment guidelines. They have explained to me in detail that there is some scientific evidence regarding the effectiveness of using convalescent plasma for treating severe/critical COVID-19 infection. They have explained to me that US FDA has approved convalescent plasma for treatment of severe COVID-19 infection. They also explained to me that at present a Phase II clinical trial is going on in India conducted by ICMR to ascertain the efficacy of convalescent plasma in COVID-19 infection. They have explained to me that convalescent plasma has been used in treatment of infections like SARS, MERS, Ebola, influenza etc

The team of doctors informed me/relative that I have developed severe/critical COVID 19 infection. They have informed me that I /patient might benefit by the compassionate use of convalescent plasma. They have clearly explained to me that convalescent plasma has not been approved for the definitive treatment of COVID-19.They have explained to me in detail that as there is no response to standard treatment administered, and as there is a risk of progression to MODS, Convalescent plasma may be used on a compassionate basis. They have explained to me about the possible side effects of convalescent plasma administration like transfusion transmitted infections [TTN], TRALI [transfusion associated lung injury], TACO [transfusion associated circulatory overload], febrile hemolytic and non-hemolytic reactions and rarely even death. They have made it clear that the standard treatment for COVID-19 will be continued irrespective of my decision regarding the compassionate use of convalescent plasma. Knowing that convalescent plasma is not an approved medication for the treatment of COVID-19, I fully agree to the compassionate use of convalescent plasma for treatment of severe/critical COVID-19 infection

Name
Relation
Sign

Institutional Medical Board Members
Name

Annexure 3 - ROLES AND RESPONSIBILITIES OF INSTITUTIONAL MEDICAL BOARD

1.The baseline clinical and biochemical parameters should be recorded in a case report form. Biochemical parameters ideally should include CRP, D-dimer, LDH, ferritin , T.protein prior to convalescent plasma administration and should be repeated every 48 hours for a week.

2.All the recorded details should be sent to State Medical board by the institutional medical board.

3.All the adverse events observed should be reported to State Medical board.

References:

1. A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease [ICMR]
2. Expanded access to convalescent plasma for treatment of COVID-19- US FDA Version 6.May 15,2020
3. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. *BMJ* 2020;;m1256. doi:10.1136/bmj.m1256
- 4 Shen C, Wang Z, Zhao F, *et al.* Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* Published Online First: 27 March 2020. doi:10.1001/jama.2020.4783
- 5 Zhang B, Liu S, Tan T, *et al.* Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest* Published Online First: 31 March 2020. doi:10.1016/j.chest.2020.03.039
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