GUIDANCE DOCUMENT ON COVID-19 CONVALESCENT PLASMA (CCP) THERAPY

Indian Society of Transfusion Medicine (ISTM)
CCP Working Group

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FOREWORD

The World Health Organization declared the outbreak of COVID-19 as a Public Health Emergency of International Concern on 30th January, 2020, and a COVID-19 pandemic on 11th March, 2020. It is a big threat to global health including India. No specific antiviral agents are currently available for its treatment. A few studies have been reported where steroids like dexamethasone, anti-HIV drugs like Ritonavir and Lopinavir, anti-malarial drugs like chloroquine and hydroxychloroquine, showed improved recovery. However, the roles are not yet clear. Another method of management of this infection is the transfusion of Convalescent Plasma (CCP) obtained from recovered COVID-19 patients to treat severely affected patients with novel corona virus.

The rationale behind this therapy is that the recovered patients have significant antibodies to SARS-CoV-2 virus which can help in disappearance of viremia. Studies have shown significant improvement in the clinical signs and symptoms and laboratory parameters after use of convalescent plasma in severely affected patients. This passive antibody administration is the only means of providing immediate immunity to susceptible persons. This approach of transfusing convalescent plasma can serve as a promising life-saving therapy for severe COVID-19 patients.
Indian Society of Transfusion Medicine felt that a Guidance document on CCP is the need of hour when Central Drugs Standard Control Organisation (CDSCO), Ministry of Health and Family Welfare, Government of India allowed the use of Convalescent plasma (off-label) in moderate COVID-19 patients who are not improving despite use of steroids.

Considering Transfusion Medicine is actively involved in the identification, selection and collection of convalescent plasma from COVID-19 recovered patients, publication of a guidance document on this aspect will be immensely beneficial to the personnel working in the Blood Centers licensed for plasma collection. This will guide to maintain a uniformity in the collection procedures of CCP throughout the country.

ISTM has created a working group of experts in Transfusion Medicine consisting of Dr Aseem Kumar Tiwari, Dr Naveen Agnihotri, Dr Aikaj Jindal, Dr C Shivaram, Dr Gopal K Patidar, Dr R. M. Jaiswal and Dr Ripal Shah to develop a Guidance Document on Convalescent Plasma collection and therapy. I am delighted to state that they prepared an advanced document on the various steps to collect, process, store and distribute convalescent plasma for Blood Centers who are into convalescent plasma collection.

I hope that this Guidance document on CCP collection and therapy would be of immense help in improving and standardizing the CCP services in the country and keep the personnel in this field updated in this specialised field of Transfusion Medicine.

Dr Debasish Gupta
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Prologue

Indian Society of Transfusion Medicine (ISTM) is a professional not-for-profit registered society representing Transfusion Medicine specialists of India.

This guidance document has been prepared by the ISTM working group on COVID-19 convalescent plasma therapy (CCP). This is based on the Drugs and Cosmetic Act1940 and rules therein (as amended till March 2020) [1], Transfusion Medicine: Technical Manual [2], guidelines from the ministry of Health and Family Welfare (MOHFW) [3] National Blood Transfusion Council (NBTC)[4,5], and Indian Council of Medical Research (ICMR)[6]. This document may be referred by all the stakeholders- plasma donors, blood banks, patients, physicians and public at large.

This document is only for the guidance purpose; it is not regulatory. The concept is to provide current knowledge in a comprehensive manner in public domain for uniformity, standardization and harmony in CCP use, in India. This document is also intended to be an enabling document endeavoring to make CCP therapy more accessible to appropriate patients. This document would be updated from time-to-time depending on new knowledge that is acquired or new regulations that are brought in.

All reasonable precautions have been taken by the ISTM working group on CCP to verify the information contained in this document. However, this document is being made available without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the information lies with the reader. In no event shall the ISTM be liable for damages arising from its use.

If you wish to provide feedback, suggestions or critique please write to the CCP group at ccp.istm@gmail.com.

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1.0. COVID-19 Pandemic

The coronavirus disease 2019 (COVID-19) pandemic, which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been associated with millions of cases worldwide with lakhs of deaths which have been directly or indirectly attributed to the infection till date. Currently, there are no approved treatments for COVID-19 disease. Supportive care along with supplemental oxygen and mechanical ventilation have been the mainstay for treatment in moderate to severe cases.

1.1. COVID-19 CONVALESCENT PLASMA (CCP) Therapy

Treatment with convalescent (a person who has completely recovered from a particular infection) plasma as a means of passive immunization has been successful in treating patients during other prior coronavirus outbreaks (i.e. SARS outbreak [2002-04] and Middle Eastern Respiratory Syndrome [MERS – 2012]). Therefore, it is hypothesized that the use of COVID-19 convalescent plasma (CCP) therapy should improve clinical outcomes in patients with moderate to severe SARS-CoV-2 infections. Use of CCP represents a virus-specific approach that can be implemented rapidly, while other disease specific therapies are still being developed. This needs to be understood by all the stakeholders that CCP therapy has been allowed currently only as an “off-label” use (unapproved indication) of plasma in COVID-19 patients by the, Government of India.

2.0. CCP DONORS

2.1. DONOR SEARCH

Blood center should identify potential CCP donors from the list of COVID-19 recovered patients and recruit them as plasma donors. Blood centers should seek help and coordination of NGO (non-government organization) working for this “cause”. Patient’s family may be advised to search voluntary non-remunerated COVID-19 recovered patient willing for CCP donation through social media

platforms amongst their 'near and dear ones' or/and through various NGO which are maintaining a data-base of the persons who have recovered from COVID-19 disease. Family members may be advised to search for blood group compatible donors fulfilling donor eligibility criteria discussed below under the heading of eligibility criteria. Extreme alertness and care have to be exercised by the blood center to prevent paid/professional donations.

2.2. ABO AND RH (D) BLOOD GROUP COMPATIBILITY

Only ABO Blood group compatibility is required in plasma donation. Rh (D)blood group can be ignored, provided anti-D antibodies are not present in Rh (D)Negative donor.

Compatibility of convalescent COVID plasma (CCP)	
Patient Blood Group	***Compatible CCP donor***
A	A, AB
B	B, AB
AB	AB
O	O, A, B, AB

2.3. ADDITIONAL MATERIAL/FACILITY REQUIRED

2.3.1. Written informed consent for donation of convalescent plasma (refer donor Informed Consent Form {ICF} ICMR template; **Annexure 1**) from the donor in addition to regular donor health questionnaire cum consent form.

2.3.2. Blood bank should possess license for plasmapheresis.

2.3.3. Blood bank/hospital should have facility to measure serum protein.

2.3.4. Blood bank should have facility to measure anti-SARS-CoV-2 IgG antibodies.

2.4. ELIGIBILITY CRITERIA FOR THE CCP DONOR

2.4.1. Males or nulliparous (to mitigate the risk of TRALI) female donors of weight > 50 kg. The donor shall be in the age group of 18 to 60 years.

2.4.2. Recovered patient (CCP donor) should preferably have had symptoms (fever, cold, cough, etc.) since there is a greater probability of presence of anti-SARS-CoV-2 IgG antibodies as compared to an asymptomatic patient. However, even asymptomatic donors may be accepted, if anti-SARS-CoV-2 IgG antibodies are present.

2.4.3. Prior diagnosis of COVID-19 disease is not mandatory since anti-SARS-CoV-2 IgG antibodies, being performed now, are direct evidence of prior COVID-19 disease.

2.4.4. Complete resolution of symptoms at least 14 days prior to donation, preferably, with one negative RT-PCR test report for SARS-CoV-2 virus infection from nasopharyngeal/throat swab,

OR

Complete resolution of symptoms 28 days prior/ post discharge. RT-PCR negative report is not mandated in this situation.

2.4.5. Donor should be advised to donate not more than twice a month. The maximum number of times that a donor can donate is twice a month/fortnightly (24 times a year).

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

3.0. BLOOD CENTER

3.1. PRE-DONATION HEALTH SCREENING AND TESTING

3.1.1. Once the donor has been administered medical history questionnaire and physical examination has been completed; donor has been found eligible, the pre-donation samples collected.

3.1.2. Blood samples are tested for complete blood counts (CBC), ABO and Rh D blood group and antibody screen, routine TTD {Transfusion Transmissible Diseases – anti HIV 1 & 2, anti-HCV, HBsAg, test for Malaria and Syphilis}, serum proteins and anti-SARS-CoV-2 IgG antibodies. The latter two tests are specifically for CCP plasmapheresis donation.

3.1.3. Total serum protein > 6gm/dl and presence of anti-SARS-CoV-2 IgG antibodies are pre-requisite for CCP plasmapheresis donation.

3.1.4. Though the DCGI document dated 01/July/2020 mentions a titer of 1:640, the working group recommends that in absence of quantitative test kits, at least the qualitative test (Yes/No) should be used for deciding upon donor eligibility. The donors with negative anti-SARS-CoV-2 IgG antibodies should be deferred.

3.1.5. It is recommended to keep a donor serum sample frozen at < -30° Celsius for a possible later date testing of titer, etc.

3.2. PLASMAPHERESIS PROCEDURE

3.2.1. Once the donor has been screened and found eligible, the plasmapheresis procedure is initiated.

3.2.2. Any automated cell separator (apheresis machine) may be used.

3.2.3. Maximum CCP Volume collection that is allowed is 500ml.

3.2.4. If the apheresis machine does not have dedicated plasmapheresis program, the plateletpheresis procedure may be modified in a manner that at least 400 ml (two therapeutic doses of 200 ml each) plasma is obtained and these is minimum possible number (and volume) of platelets are collected. This by-product (where platelets are collected separately and later on suspended in the plasma) may be discarded or returned to the donor (depending on the cell separator). The maximum volume that can be collected in one session is 500 ml.

3.2.5. The minimal labelling requirement on the plasma bag would be as follows:

- Unique identification number
- ABO blood group
- TTI screening negative results
- Name of the product: COVID-19 CONVALESCENT PLASMA
- Date of Collection (dd/mm/yyyy)

- Date of Expiry (dd/mm/yyyy)
- Volume of the product (in ml)

3.3. STORAGE OF THE CCP PRODUCT

3.3.1. CCP has to be stored at temperature < -30° Celsius.

3.3.2. The unit may be quarantined in “un-tested” if any test result is pending. It should be moved to “tested” compartment once the testing results are satisfactory.

3.3.3. Separate shelf of deep freezer {or if possible, separate deep freezer} may be dedicated for CCP.

4.0. CCP RECIPIENT

4.1. RECEIVING OF CROSS-MATCH REQUEST AND PATIENT’S SAMPLE

4.1.1. Patient’s request form for CCP is received. The blood group is performed, if not done previously {it is a good practice to perform group and screen for all patients at the time of admission}.

4.1.2. A separate consent form (besides regular consent that is part of hospital/blood bank protocol) is required (refer patient Informed Consent Form {ICF} ICMR template; **Annexure 2)**.

4.1.3. The request form should mention “off-label” use of CCP.

4.1.4. A blood component requisition by a qualified physician, from another designated COVID-19 treatment hospital or a hospital treating COVID-19 patient may also be accepted.

4.1.5. The CCP of a particular blood group stored in a blood bank may be transferred or exchanged with another licensed blood center, depending on actual need {advised by physician}. Appropriate documentation including blood component transfer records should be maintained by both the licensed blood centers.

4.2. THAWING AND CROSS-MATCHING THE CCP UNIT

4.2.1. The plasma unit is thawed at 37^0 Celsius and the plasma bag segment is used for minor crossmatch with patient's RBC (red blood cells).

4.2.2. The minor crossmatch using donor plasma and patient red blood cells is performed

4.2.3. If the unit is crossmatch compatible, the unit is issued with minimum labelling requirements as follows:

- Name and unique ID of patient
- Unique ID of the unit
- ABO blood group of the patient and CCP Unit
- Date of issue (dd/mm/yyyy)
- Name and ID of the technical person who performed the crossmatch

4.3. CLINICAL USE OF CCP THERAPY

4.3.1. It is important to select the patient appropriately. Only moderately affected patient {defined below} have been shown to benefit from the CCP therapy. Patient should be provided CCP therapy if:

- ICMR definition: Patients admitted with RT-PCR confirmed COVID-19 illness and has either PaO2/ FiO2: 200-300 OR Respiratory Rate > 24/min and SaO2 < 93% on room air
- MOHFW definition: Adolescent or adult with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute/Child with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range90-94%) on room air, Respiratory Rate more or equal to 24 per minute.

4.3.2. Moderate disease with increasing oxygen requirements not responding to steroids should receive CCP therapy {should be instituted before the patient goes into multiple organ failure}.

4.3.3. Patient should not have history of Ig A (immunoglobulin A) deficiency syndrome or allergy to immunoglobulins.

4.3.4. One or two therapeutic units of 200-250 ml each should be administered to the patients on two consecutive days (24 hours apart and if, first is tolerated well), depending on the patient condition. It is advised that donor CCP units provided to patient should preferably be from two different donors.

4.3.5. Patient should be closely monitored for adverse effects of plasma and appropriate intervention should be instituted, if needed

4.3.6. CCP therapy may be given along with other therapies like, Remdesivir, Tocilizumab, etc.

4.3.7. Patient should be monitored for improvement/deterioration after CCP therapy.

4.4. PATIENT'S SAMPLE STORAGE

The patient's sample has to be stored for seven days at 4^0 Celsius. Donor's sample may be archived at < -30^0 Celsius for future testing

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