

## **Protocol for the use of convalescent plasma for the treatment COVID-19 infected patients**

**Background:** In December 2019, a cluster of patients with pneumonia of unknown cause was reported in Wuhan, China [1]. The causative pathogen was subsequently identified as severe acute respiratory syndrome–related coronavirus-2 (SARS–CoV-2) [2], a newly described betacoronavirus. The epidemic spread rapidly worldwide within three months and was declared as a pandemic by WHO on March 11,2020 [3]. As of April 18<sup>th</sup>, 2020, a total of 2,243,512 confirmed cases and 154,209 related deaths had been reported worldwide. In Qatar as of the same date, 4,663 cases of confirmed cases have been reported with 7 related deaths.

Beyond supportive care, there are currently no proven treatment options for coronavirus disease (COVID-19) and its related pneumonia. Several therapies, such as Remdesivir and Favipiravir, Lopinavir/ritonavir and Hydroxychloroquine are under investigation, but the antiviral efficacy of these drugs is not yet known and need to be explored [5].

Human convalescent plasma (CP) has been successfully used for other infection prevention and treatment and thus may provide an option for treatment of COVID-19 and could be rapidly available from people who have recovered from disease and can donate plasma.

Prior experience in SARS and severe influenza suggests that CP may be considered for patients who are deteriorating despite other specific and supportive therapy and in whom the virus remains detectable [6-10]. A meta-analysis from 32 studies of SARS coronavirus infection and severe influenza showed a statistically significant reduction in the pooled odds of mortality following CP therapy, compared with placebo or no therapy (odds ratio, 0.25; 95% confidence interval, 0.14-0.45)[12]. One randomized clinical trial (RCT) in critically ill influenza A (H1N1pdm09)-infected patients found a survival benefit when hyperimmune globulin was administered within 5 days of symptom onset [13]. Convalescent serum was also used in the 2013 African Ebola epidemic. A small non-randomized study in Sierra Leone revealed a significant increase in survival among those treated with convalescent whole blood relative to those who received standard treatment [14]. Since the virological and clinical characteristics share similarity among SARS, MERS, and COVID-19, CP therapy might be a promising treatment option for COVID-19 rescue. Patients who have recovered from COVID-19 with a high neutralizing antibody titer may be a valuable donor source of CP.

The mechanism of action by which passive antibody therapy would mediate protection is viral neutralization. However, other mechanisms may be possible, such as antibody dependent cellular cytotoxicity and/or phagocytosis [15].

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a COVID-19 susceptible person, this antibody will circulate in the blood, reach tissues and mitigate infection severity. Depending on antibody amount and composition, the protection conferred by transferred immunoglobulin can last from weeks to months.

A challenge in using convalescent plasma, namely, that some who recover from viral disease may not have high titers of neutralizing antibody. Of note, analysis of convalescent sera from 99 MERS survivors showed that only 87 had neutralizing antibody with a geometric mean titer of 1:61. This suggests that antibody declines with time and/or that few patients make high titer responses [16]. A theoretical risk of the use of convalescent plasma involves the phenomenon of antibody-mediated enhancement of infection (ADE). ADE can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several

mechanisms for ADE have been described and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain [17]. It may be possible to predict the risk of ADE of SARS-CoV-2 experimentally, as was proposed for MERS. Since the proposed use of convalescent plasma in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely. Evidence from the use of convalescent plasma in patients with SARS1 and MERS, and anecdotal evidence of its use in patients with COVID-19 suggest it is safe [18]. Nevertheless, caution and vigilance will be required for any evidence of enhanced infection.

Experience with the use of convalescent plasma in patient with COVID 19 infection is very limited. Literature search revealed three reports of using convalescent plasma in patients with severe COVID 19 infection.

In the first report from china, Shen et al, reported a case series of 5 critically ill patients with COVID-19 and ARDS[19]. Administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The criteria for use of convalescent plasma in these patients was severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; PAO2/FIO2 < 300 and mechanical ventilation. In another case series from China, Duan K et al, in a series of 10 adults with severe COVID 19 infection, one dose (200 mL) of CP was well tolerated and could significantly increase or maintain the neutralizing antibodies at a high level, leading to disappearance of viremia in 7 days[20]. Clinical symptoms and paraclinical criteria rapidly improved within 3 days. Radiological findings showed varying degrees of absorption of lung lesions within 7 days. They conclude that their results indicate that CP can serve as a promising rescue option for severe COVID-19. In a third report from Korea, Ahn JY et al, treated two patients with COVID-19 with convalescent plasma infusion [21]. Both patients presented severe pneumonia with acute respiratory distress syndrome. Both patients showed a favorable outcome after the use of convalescent plasma in addition to systemic corticosteroid.

We plan to conduct a 2-phase intervention. In the first phase (CP collection phase), we will explore the feasibility of collection of CP from donors who have significant titers of anti-SARS-CoV 2 antibodies. In the second phase, patients with COVID-19 infection will be treated with CP.

## **Methods**

### **CP collection phase**

The inclusion criteria for screening potential CP donors include individuals from the following cohorts:

- 1- Prior diagnosis of COVID-19 documented by a laboratory test
- 2- Complete resolution of symptoms at least 28 days prior to donation

OR

- 3- Complete resolution of symptoms at least 14 days prior to donation AND

Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood

- 4- Male donors. Female donors are not accepted to minimize the risk of transfusion-related acute lung injury (TRALI)

5- Defined SARS-CoV2 neutralizing antibody titers, if testing can be conducted (optimally greater than 1:80)

### **CP therapy phase**

We will screen consecutive critically ill patients admitted to the intensive care unit or other areas of the hospital where critically ill patients receive care for the following criteria:

#### **Inclusion criteria**

1. Laboratory-confirmed COVID-19 infection.
2. Must have severe or immediately life threatening COVID-19 infection
  - a- Severe Disease defined as:
    - 1-Dyspnea
    - 2-Respiratory frequency >30/min
    - 3-Blood oxygen saturation < 93%
    - 4-Partial pressure of arterial oxygen to fraction of inspired oxygen ration ,300
    - 5-Lung infiltrate >50% within 24 to 48 hours
  - b-Life threatening disease is defined as:
    - 1-Respiratory failure requiring mechanical ventilation
    - 2-Septic shock
    - 3-Multiple organ failure including receipt of renal replacement therapy or extra-corporeal life support.
3. Age of more than or equal to 18 years.
4. Provide informed consent

#### **Exclusion criteria**

1. Negative RT-PCR from respiratory secretions
2. History of allergic reaction to blood or plasma products (as judged by the investigator).
3. Medical conditions in which receipt of 500 mL intravascular volume may be detrimental to the patient (e.g., actively decompensated congestive heart failure).
- 4-Severe multi-organ failure, hemodynamic instability.
- 5-Other documented uncontrolled infection.
- 6-Severe DIC needing factor replacement, FFP, cryoprecipitate.
- 7-Expected survival for less than 48 hours

#### **Informed consent**

The protocol coordinator and/or the treating physician will explain the objectives of this intervention and its potential risks and benefits to the donor or patient (or to his/her surrogate decision maker) and will obtain the following consent forms in and as appropriate:

#### **CP collection phase**

1. Consent for COVID-19 serologic testing and COVID-19 RT-PCR for donors.
2. Consent for CP donation for those who have elevated anti- SARS-CoV-2 titers as described below.

## **CP therapy phase**

1. Consent for enrollment in the CP therapy phase.

## **Protocol procedures For the CP collection phase**

1. Eligible candidates for CP donation (as per the inclusion and exclusion criteria above) will be approached to have their blood tested for anti- SARS-CoV-2 serology. Subjects who are seropositive will be screened subsequently for SARS-CoV-2 RT-PCR to exclude active infection.
2. Subjects with anti- SARS-CoV-2 specific titer  $\geq 1:80$  and no clinical (not requiring medical support for respiratory or other organ function) or laboratory (rRT-PCR negative) evidence of COVID-19 infection will be screened for eligibility for plasma donation according to the standard criteria in accordance with the WHO Guidelines Assessing Donor Suitability for Blood Donation
3. Those who meet the plasma donation criteria will be invited for donation.

Plasma may be collected by apheresis (500 or 600 ml based on weight), as appropriate for the individual donor. Collection will be performed by trained blood bank staff operating under the standard operating procedures in certified facilities. The collected frozen plasma will be stored in the blood bank after being tested for serology of hepatitis B and C viruses (HBV and HCV), human immunodeficiency virus (HIV), malaria, syphilis and human T-lymphotropic virus (HTLV) types I and II and nucleic acid testing (NAT) for HBV, HCV and HIV according to international guidelines.

## **For the CP therapy phase**

1. Critically ill COVID-19 patients who meet the above patient eligibility criteria will be approached for consent.
2. Patients will have their blood type determined. CP must be ABO compatible with the recipient's blood type.
3. The intervention includes the administration of 2 units of CP. Each unit of plasma (200 -250 ml) will be given over 2 h with an interval of 1 h between the two units. Plasma transfusion will be done in accordance with the standard policies for administration of blood products.

## **Co-interventions**

The clinical team will have full, independent control of patient management and as such, management other than CP therapy will not be influenced by the intervention team. Co-interventions, including use of hydroxychloroquine, Azithromycin, Kaletra or Darunavir/cobicistat, corticosteroids, ribavirin, Tocilizumab and interferon, will be documented on the case report forms.

Frequency and duration of follow-up Clinical and laboratory data will be collected at baseline, days 1, 3, 5, 7, 14, and 28 after CP administration.

**Outcome measures:****CP collection phase:**

We will explore the feasibility of the intervention, as measured by ability to screen potential plasma donors, and derive sufficient plasma to enrol 100 patients in a 6 months period. We will also qualitatively describe logistical challenges experienced through the conduct of this intervention, including ethical, administrative and regulatory challenges.

**CP therapy phase:**

1. We will establish safety of the study intervention, as measured by number of serious adverse events related to the intervention (adverse events include development of complications of intravascular volume overload and clinical pulmonary edema by temporally related-shortness of breath, chest radiograph findings and change in oxygenation requirements; development of transfusion-related acute lung injury (TRALI) or substantial allergy or anaphylaxis). These serious events will be adjudicated by the protocol team.

**2-Clinical Outcomes:**

We will measure

1. Sequential organ failure assessment (SOFA) scores on days 1, 3, 5, 7, 14, and 28.
2. Ventilatory free days.
3. ICU mortality and LOS
4. Hospital mortality and LOS
5. Multi-organ failure (and other ICU support e.g., dialysis, vasopressors)

**Laboratory Outcomes:** We will measure the following laboratory outcomes:

- 1-Virological clearance at day 7, 14, 21
- 2-CT values for SARS-CoV-2 PCR positivity (RT-PCR) at days 0, 7,21 when available.
- 3- Anti-SARS-CoV-2 titers at days 0 and when available

**Safety measures**

In the event of an acute transfusion reaction, the transfusion will be stopped immediately and must be reported to the blood bank the principal investigator immediately as well as to the study management committee. All the serious adverse events (SAE) adjudicated as related to the intervention will be recorded.

## References

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