

# Convalescent Plasma Therapy Against Covid-19: A Comprehensive Review

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**Abstract:** *The pandemic COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) continues to create havoc all over the world having caused more than 40 million cases and more than 11,32,528 deaths worldwide as of October 21, 2020. The treatment of COVID-19 is proving to be a challenge to the medical fraternity worldwide with no specific drug therapy or vaccine available in sight. The use of Convalescent plasma (CP) therapy, a form of passive immunization, in the treatment of COVID-19 has been gaining ground all over the world including India as convalescent plasma therapy has been used previously in virus infections like MERS-CoV, SARS-CoV, H1N1 and other viral infection with some success, when the situation was similar as in any infectious outbreak situations. This review looks at CP therapy as a possible treatment option for COVID-19 in terms of: type of antibodies in the convalescent plasma, mechanism of action, possible adverse effects, current approval status and its limitations in the management of COVID-19.*

**Key words:** *Convalescent Plasma, Passive Immunization, COVID-19, SARS-CoV-2, Plasma therapy, Antibodies.*

## 1. INTRODUCTION

COVID-19 – corona virus disease is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This has been causing a global distress since its first origin in Wuhan city, Hubei province of China in December 2019. On March 11 2020, WHO declared COVID-19 as a pandemic as by then it had 118,000 cases in 114 countries and 4291 people had lost their lives[1]. It is a zoonotic infection and the corona virus belongs to the genera *betacoronavirus*. It has 82% similarity to the SARS-CoV which is the causative agent of SARS in 2002[2]. These enveloped viruses contain single stranded positive sense RNA. They

have structural proteins like Envelope(E), with glycoprotein spikes (S), Matrix (M), Nucleic capsid (N) along with non-structural proteins RNA-dependent RNA polymerase (RdRp), open reading frames ORF1a and ORF1b and hemagglutinin-esterase (HE)[3].

The S glycoprotein helps the virus to bind to the ACE 2 receptors present on the lung, kidney and gastrointestinal tissue[4]. The virus gets attached to the nasopharyngeal epithelial cells, multiplies within it and then descends to the lower respiratory tract. A good immunity helps to limit the disease in the incubation and asymptomatic stage. Like in any other viral infection the inflammatory cells will be stimulated and activated. The T cells of cell mediated immunity and the B cells of humoral immunity are activated. In certain genetically predisposed individuals the cytokines, chemokines and the cell activation mechanism will be exaggerated[5]. This gives rise to cytokine surge causing increased macrophage activation and the acute respiratory distress syndrome (ARDS). The antibodies against the S protein neutralize the binding of the viral particles to the ACE 2 receptors which stops the infection of fresh cells.

The treatment of the COVID-19 patients poses a challenge to the medical fraternity. Absence of specific antiviral agents or vaccines to prevent the further spread of the infection has forced the use of non-pharmacological approach of treatment in such patients. This includes maintenance of ventilation, low dose corticosteroids and fluid management[6]. A cocktail of antivirals which were previously effective in case of SARS-COV and MERS-COV, H1N1 have been tried. During an ongoing pandemic it would be difficult for any research activity to provide, cost effective, safe and potent vaccine to limit the spread of the infection. In case of newer antiviral discovery, it takes minimum of 10 years for any drug to go through the process of research and development, pass clinical trials and be ready for use[7]. This may not be of much interest to the pharma companies as these viral infections last till there is development of herd immunity. Though the infection may lurk and cause pockets of surges in the following years the vaccine or the antiviral market may not be very profit worthy. The multiple forms of treatment options are being explored by rapid scientific collaborations with World Health Organisation taking an active part (SOLIDARITY) through a large global trial for antivirals and vaccines against COVID -19[8].

The concept of passive immunity has been known and used in many of the infective and non-infective disease conditions. Here the individual is given antibodies artificially rather than actively developing the antibodies by immune response. This helps to prevent or treat a person who is not protected from the infection. Man has used the concept of passive immunity against infections like diphtheria, tetanus, rabies, hepatitis B virus infection to name a few. The human or animal source of the antibodies provide for polyclonal antibodies which may not be specific for certain epitopes. This can be overcome by using monoclonal antibodies which are tailor made for specific epitopes of known pathogen[9]. The efficacy will be better. Here again the production of monoclonal antibodies and its clinical trial will take long time before which the pandemic may die its own death. Convalescent plasma (CP) therapy has been used previously in virus infections like MERS-COV, SARS-CoV, H1N1, H5N1, H7N9 virus infection including the current SARS-CoV2 when the situation was similar as in any such pandemic outbreaks[10]. [Table 1]

This is the plasma recovered from the patients who have recuperated from the illness. It contains the polyclonal antibodies against the targeted pathogen.

A CP therapy along with high dose methyl prednisolone have shown favorable response where antiviral agents have failed to improve the prognosis of SARS[21]. Comparing different treatment protocols neutralizing antibodies have benefits such as no drug resistance development which is hindering factor when there has been usage of neuraminidase inhibitors or adamantines due to viral mutations.

## **2. TYPE OF ANTIBODIES:**

Neutralizing antibodies against SARS-CoV2 might likely work better for therapy. Although it's yet unclear whether total antibodies or the sub class of antibodies (IgG, IgM or IgA) could be given as a means of treatment,[22,23] some studies have suggested that a higher levels of Ig G against S1 protein with titres >4 was significantly associated with a better outcome[24]. A validated test like ELISA or others tests is required to measure the antibody titre [25]. In one study, the development of antibodies namely IgG, IgM, IgA in SARS associated Coronavirus infection reached peak after around a mean of 15days and lasted for > 3 months with a titre of 1:800 IgG antibodies [26].

The timing of collection of plasma is crucial to get required titre of antibodies from the donors. Seroconversion coupled with high titre of antibodies occurs after greater than 14 days following onset of signs and symptoms[11]. FDA recommendation for donor requires with antibodies of 1:160 titre; and one with a titre of 1:80 as an alternative only when no other matched unit is available[27]. Therapy initiated in the early days of onset of symptoms of infection has better prognosis and reduces viral load. It has been proven in the past about the safety in procedure and reduced mortality[14, 28].

## **3. MECHANISM OF CP:**

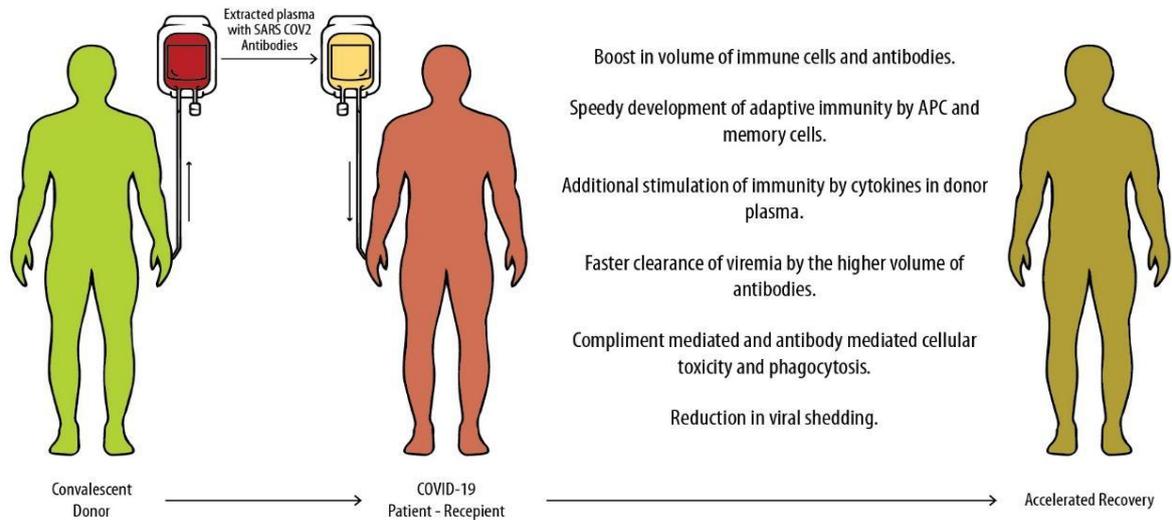
Multiple hypothesis has been proposed to explain the probable mechanisms underlying the rationale of using the convalescent plasma from survivors in the treatment of COVID-19 patients.

These include:

- a) Injected immune cells and antibodies boost the immunity by volume effect.
- b) The reduction of the effective time taken for the development of innate/adaptive immunity as viral antigens already being in presentable state by the antigen presenting cells in the donor's plasma and the role of memory B cells.
- c) The role of cytokine induced immune stimulation is accelerated by the cytokines already present in the donor's plasma.

Based on the second hypothesis, selective leukapheresis and transfusion is also proposed for the treatment of infections like Ebola, Spanish flu etc[29]. Another view was that the antibodies suppressed viremia and helped in clearance of virus by the host[31, 32]. In vitro studies have shown that neutralizing and non-neutralizing antibodies help in elimination of virus infected cells of HIV1 infection[32]. Retrospective data analysis of the patient outcome of SARS 1 infection, in a study, revealed that convalescent plasma given early in the disease course fared better than those who received antivirals and steroids alone[33]. Few other studies have concluded that apart from the antibodies binding and neutralizing the pathogen directly, complement mediated and antibody mediated cellular cytotoxicity as well as phagocytosis might contribute to the effective healing effect[34-36]. Additionally light was thrown by a study on six critically ill SARS-CoV-19 patients who received convalescent plasma therapy, that there was reduction in the viral shedding by the host, both in survivors and non-survivors. Institution of the therapy at the right time point before 14 day of therapy in those with potential to become critically ill later, was a requirement to prevent fatality [37]. [Figure 1]

Figure 1 : Mechanism of convalescent plasma therapy from a convalescent COVID-19 donor to a



#### 4. COVID-19 POSITIVE RECIPIENT.

##### *Approval status:*

On 26 day of March 2020, FDA approved the use of convalescent plasma from donors recovered from COVID-19 infection in the treatment of critical COVID-19 infected patients[27]. This was after consideration of the past experiences in the management of patients with H1N1, SARS and MERS[31-32, 38-43]. The CP treatment is considered under the investigation new drug (IND) status or as expanded government led clinical trial based on a master protocol. The access was provided only for patients defined as having serious or life threatening COVID-19 infections and not for prophylaxis[27].

Currently in many countries including India, the government has permitted hospitals this mode of therapy within the purview of clinical trials only after registering in the regional Clinical Trials Registry[44].

Potential indications for CP therapy would include

1. Prophylaxis for asymptomatic individuals in close contacts or close proximity with CoVID-19 patients without personal protective equipment(PPE) and those asymptomatic but at-risk individuals due to co-morbid conditions, health care workers (frontline workers), immunocompromised state.
2. To evaluate treatment efficacy in pandemics.
3. To check whether the form of therapy helps manage individuals with mild, moderate, severely ill requiring ventilator support and high risk pediatric population who have been tested positive for SARS-CoV2[34].

## **Flow chart for plasma extraction according to FDA.[Figure 2]**

### ***Adverse effects:***

The risks associated with plasma therapy include those associated with general blood transfusion like the transfusion transmitted infections and immunological reactions such as allergic reactions or serum sickness. These risks remain at low profile given the modern methods for screening for the transfusion transmitted infections and the cross matching techniques[30, 45].

Being a relatively new pathogen whose pathogenic complications and multitude of manifestations are slowly being unveiled, reports from Wuhan, China have described that the SARS-CoV-2 has thromboinflammatory response and thus is itself thrombogenic. The reason quoted is that it could be due to the lack of prior immunity to the new virus leading to a massive unhindered inflammatory response resulting in coagulopathy[46]. Thrombotic risk is rare yet serious complication with the use of immunoglobulins. It ranged from 0.4 to 14.9% depending on the product[47, 48]. In light of this we need to carefully weigh the benefits of plasma in mitigating the possible viral mediated thromboinflammatory response versus possible thrombotic risk posed by immunoglobulin therapy which would be possible to monitor if the therapy is part of a clinical trial.

Transfusion associated lung injury (TRALI) is another adverse event expected in plasma transfused patients already with compromised lung function[44]. This occurs usually within 6 hours of transfusion and mediated by the antibodies against HLA antigens. This should be carefully assessed for the risk benefit ratio. The risk of TRALI could be avoided if the donors are preferably chosen to be male and females who have never been pregnant nor have had any abortions. This way the risk of presence of antibodies to HLA antigens and leukocytes could be mitigated[49].

Transfusion associated circulatory overload (TACO), a potential adverse effect, in a patient already with acute lung injury due to COVID-19[50] can possibly be mitigated by the usage of diuretics before transfusion, slow rate of transfusion and close monitoring [51]

Other risk include antibody dependent enhancement of infection (ADE) that have been demonstrated with SARS-1, MERS[45, 52]. and several other viruses[51]. This may prompt concerns in hyper immune globulin therapy using pooled plasma from convalescent COVID-19 cured patients. This is known with sub neutralizing levels of antibodies. But this is unlikely with COVID-19 due to high titres of neutralizing antibodies during the epidemic[45]. The innate and adaptive immune response occurring by natural infection is likely to be more robust both qualitatively and quantitatively due to induction of the cytokines and chemokines as well as due to strong antigenicity of the wild strain of SARS-CoV-2 as compared to vaccine induced immunity. Anti-inflammatory response could be generated due to total and neutralizing antibodies binding to the inhibitory receptors thus mitigating the risk of antibody mediated immunopathology[53].

In studies done in China on critically ill COVID-19 patients, no adverse effects were reported [36, 54, 55]. Anecdotal evidence from China on limited 245 COVID-19 patients has proven convalescent plasma transfusion to be safe with no reported adverse reactions[45]. Another observational study on 10 patients during and after plasma therapy for COVID-19 did not report any adverse event[11] Despite the known adverse effects, in the event of pandemic and with past experiences with that for other infections the benefits seem to outweigh the risks mentioned. However randomized control trials may unveil the true picture of unexpected adverse events, if any.

## 5. LIMITATIONS OF CP COLLECTION:

One challenge being tracing and recruiting donors for collection of plasma. Two, could be the unwillingness of the donor to donate plasma because of not having donated blood over many years, no remuneration or poor recovery after infection. Third could be the limitation due to not satisfying donor eligibility criteria to donate for COVID-19 patients[56].

In developing countries like India, convalescent plasma therapy has not been tried in any emerging viral infections. The approval from drug controller general of India (DCGI) for collection of plasma from recovered COVID-19 positive patients is a mandatory requirement. The donor blood can be collected only in centers approved by DCGI [44].

## 6. CONCLUSION:

In the advent of cases presenting with new signs and symptoms, it becomes necessary to identify that it is due to new pathogen and as the number of cases increase the rise of supportive treatment is the only option available. The outcome of the disease condition could be mortality, recovery with disability or complete recovery. As the experience increases the chance of search and success or failure of treatment options: antimicrobials or vaccines is noted in any disease pattern. The discovery of antimicrobials or vaccines may take considerable time, at a cost and interest from investors. During this period if the number of cases are increasing the plasma from the recovered patients may be effectively used as the main line of treatment. Close monitoring of the course of events during CP therapy as part of ongoing randomized clinical trials in the current COVID-19 pandemic would give more substantial evidences on the risk-benefit ratio.

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### **Method used for locating, selecting, extracting and synthesizing the data:**

A team of five authors was involved in the literature search using PUBMED, EMBASE and GOOGLE SCHOLAR for over a period of one month and the articles were reviewed. Following the review a sketch was drawn to extract the relevant information depending on the consensus from all the authors. The script was written by in portions by the authors and later reviewed by all the five with inputs and corrections before agreeing upon the final manuscript.

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DISEASE	NAT <sup>a</sup> (TITRE)	CP <sup>b</sup>	OUTCOMES	ADVERSE EFFECTS	STUDIES
<b>SARS-CoV2</b>	1:640	200 ml	In severe patients, improvement in clinical and preclinical criteria in 3 days Inconclusive outcome and recommendation of more trials.	More trials recommended	Kai Duan et al, <sup>[11]</sup> Jin Young Ahn et al <sup>[12]</sup>  Stockman LJ et al <sup>[13]</sup>
<b>SARS-CoV</b>	Not known	200 - 400 ml	Favourable in patients with PCR positive and seronegative for the virus but poor outcome in PCR positive and seropositive. Mortality ranges from 7-23%. Early treatment beneficial	No side effects <sup>[14]</sup>	Cheng Y et al <sup>[15]</sup>  Jenkins et al <sup>[14]</sup>
<b>MERS-CoV</b>	1:160	Not known	Favourable outcome in 3 patients.	Acute Lung injury <sup>[16]</sup>	Jae-Hoon Ko et al <sup>[17]</sup>
<b>H5N1</b>	1:80	200 ml (3 doses)	Reduced viral load and CXR densities in 12 hours No significant benefits, No deaths reported, recommending early treatment	No adverse side effects reported <sup>[14]</sup>	Zhou B et al <sup>[18]</sup>  Jenkins et al <sup>[14]</sup>
<b>H1N1</b>	1:160 or more	500 ml	Reduced respiratory tract viral load, serum cytokine response, and mortality. Reduction by 21% in case fatality rates. Recommending early therapy	Chills, sweats, rise in temperature after infusion <sup>[14]</sup>	Hung IF et al <sup>[19]</sup>  Jenkins et al <sup>[14]</sup>
<b>H7N9</b>	1:80 or more	200 ml	Patient on follow up had improved LFT, and normalized blood counts	No adverse side effects known	Xiao-Xin Wu et al <sup>[20]</sup>

a - Neutralizing Antibody titre; b- CP-Convalescent Plasma

Table 1: Studies describing the outcomes and adverse effects during various viral disease outbreaks.

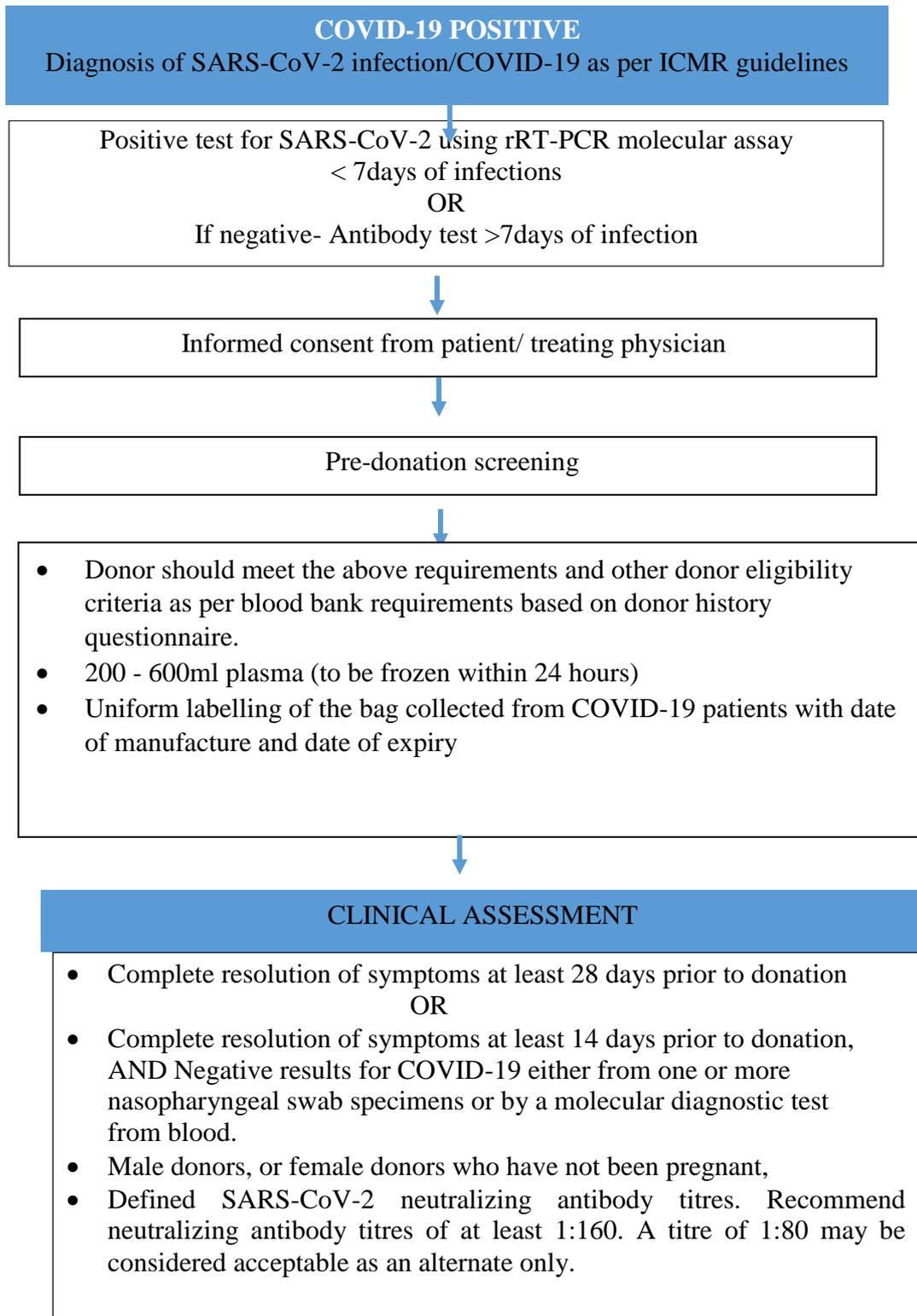


Figure 2 : Flow chart of the steps involved in CP extraction according to FDA

**Figure 1 Mechanism of convalescent plasma therapy from a convalescent COVID-19 donor to  
a  
COVID-19 positive recipient. APC: Antigen presenting cell**