



## **Convalescent Plasma Therapy in COVID 19 an Indian Scenario: Comprehensive Review**

**Shruti Vimal<sup>1\*</sup>, Pratiksha Naval<sup>1</sup>, Manoj Sawadker<sup>1</sup>, Pallavi Bhomia<sup>1</sup>,  
Neha Jadhav<sup>1</sup>, Shraddha Yadav<sup>2</sup>, Madhura Bhosale<sup>2</sup>, Arpana Dharwadker<sup>3</sup>  
and Vidya Viswanathan<sup>3</sup>**

<sup>1</sup>*Department of Pathology, Symbiosis Medical College for Women, Symbiosis (Deemed) International University, Lavale Pune 412115, Maharashtra, India.*

<sup>2</sup>*Department of Pharmacology, Symbiosis Medical College for Women, Symbiosis (Deemed) International University, Lavale, Pune 412115, Maharashtra, India.*

<sup>3</sup>*Department of Pathology, D Y Patil Medical College and Research Centre, DPU, Pimpri, Pune 411027, India.*

### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/JPRI/2021/v33i44B32697

#### Editor(s):

(1) Dr. Takashi Ikeno, National Institute of Mental Health, National Center of Neurology and Psychiatry, Japan.

(2) Dr. Syed A. A. Rizvi, Nova Southeastern University, USA.

(3) Dr. Sung-Kun Kim, Northeastern State University, USA.

#### Reviewers:

(1) Laura Arruda Costa, Metropolitan Academic Center of the Amazônia, Brazil.

(2) Manal El Said, Theodor Bilharz Research Institute, Egypt.

(3) Yatin Talwar, AIIMS, India.

Complete Peer review History: <https://www.sdiarticle4.com/review-history/74533>

**Review Article**

**Received 22 August 2021**

**Accepted 22 September 2021**

**Published 25 September 2021**

### **ABSTRACT**

The recent pandemic due to Corona virus more popularly known as COVID 19 has reassessed the usefulness of historic convalescent plasma transfusion. (CPT) The CPT is one of the promising therapies in the current pandemic situation. This review was conducted to evaluate the effectiveness of CPT therapy in COVID 19 patients based on the publications reported till date. PubMed, EMBASE and Medline databases were screened up to 30 April 2021. All the records were screened as per the protocol eligibility criteria.

The main features of the studies reviewed were, convalescent plasma can reduce mortality in severely ill patients, an increase in neutralizing antibodies titre and disappearance of SARS CoV 2

RNA was observed in all the patients on CPT therapy and over all a beneficial effect on clinical symptoms after administration of CP.

Based on the review findings and the limited scientific data, CPT therapy in COVID 19 patients appear safe, clinically effective and reduces mortality. However, the need of a multicentre clinical trials, unequivocal proof of efficacy, effectiveness and the need for the standardisation of the CPT needs to be addressed immediately for the full utilisation of potential of CPT.

**Keywords:** *Convalescent plasma therapy; COVID 19; Neutralizing Antibodies; SARS COV 2; anti SARS CoV 2 antibodies; donor selection; Passive immunization.*

## 1. INTRODUCTION

Convalescent plasma (CP) therapy has a long history, of about 100 years. A team of two scientists, Behring and Kitasato had discovered that graduated dose of sterile broth cultures of tetanus and diphtheria bacilli, produced antitoxins, this was first published in 1890. Later in 1898, Behring and F. Wernicke found that lifelong immunity to diphtheria could be provided with the advent of diphtheria toxoid. The setup, actually opened doors for “serum therapy”. In the current scenario, the treatment of new COVID 19 cases has been done by convalescent plasma therapy, which helps in building the immunity and viral neutralization against the disease [1-4]. The first approval of CP was from FDA on March 24, 2020, in which all critically ill COVID 19 patients in NYC and Houston received experimental treatment. Similar studies were conducted in China, the subjects who had undergone the therapy showed shortening of duration of symptoms, with improved oxygen levels and a drop in viral load. However, the efficiency of this method did not exceed 80% (the percentage of survivals) in curing COVID-19 patients, thus, it is not the best method, but it worked well [5]. In India, the Drug Controller General of India, gave its approval to a proposal by the ICMR for the clinical trial of CP in Covid 19 patients, at a meeting held on April 13, 2020 [6].

## 2. HISTORY

CP therapy has been used before in treatment of mumps, measles, polio and flu, before the advent of vaccines. In 1901, an Italian physician Francesco Cenci have used convalescent serum as therapeutic tool in children against measles, in an outbreak of mumps and prevention of testicular complications [7]. Hess had used the same therapeutic measures in 1915 [8]. Its usage has been well documented in history during outbreak of many diseases at various periods including Spanish Influenza A (H1N1) infections in 1915 to 1917 [6]. New York had

witnessed the polio outbreak in 1916 and CP therapy was used for treatment of acute paralysis secondary to poliomyelitis [9]. Nicoll and Conseil in 1916 applied sera-therapy to contain the measles epidemic in Tunis [10]. To count, severe acute respiratory syndrome SARS in 2003, pandemic 2009 influenza A (H1N1), Avian influenza A (H5N1), several other haemorrhagic fever such as Ebola and other viral infections have shown remarkable response. As an add on, studies have shown that CP antibodies can limit the virus reproduction in the acute phase of infection and help clear the virus, which is absolutely needed for early recovery from the disease. However, it showed no response in Ebola infection, a study conducted in 84 patients had concluded these findings [11].

## 3. IMMUNOLOGICAL ASPECTS OF COVID 19

CP therapy is bought about by collecting plasma from an individual who has recently recovered from infection and infusing it into an at risk individual. The plasma contains several humoral factors capable of providing immunity, but the most important one is believed to be the polyclonal antibodies against the target agent. It confers immune-protection by numerous mechanisms. Fig. 1 Direct viral neutralization by neutralizing antibodies (N Abs) and the immunomodulatory actions that limit host damage are important mechanisms in COVID-19 [12-14].

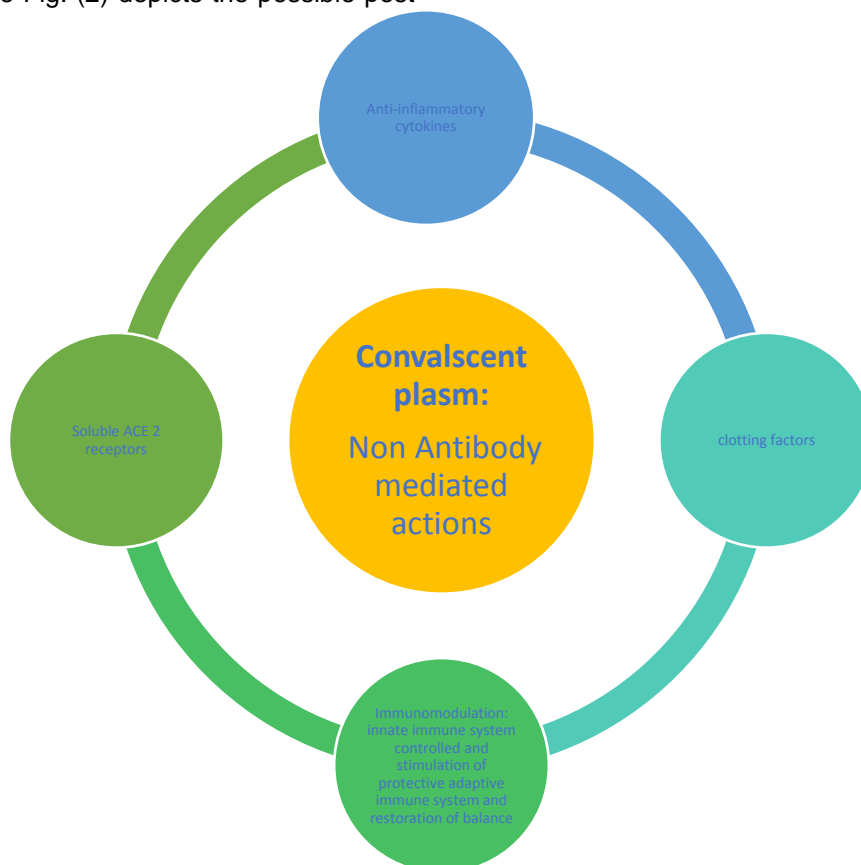
It's used for induction of passive immunity [15]. Immunological studies have also demonstrated a diverse antibody repertoire in the serum of recently recovered patients. Antibodies directed against the receptor binding domain of the viral spike protein (SRBD), bind them, limit cell entry and inhibit the viral amplification [16-18]. Laboratory studies have shown potent neutralizing activity by such antibodies repertoire against the live virus. This can decrease the viral

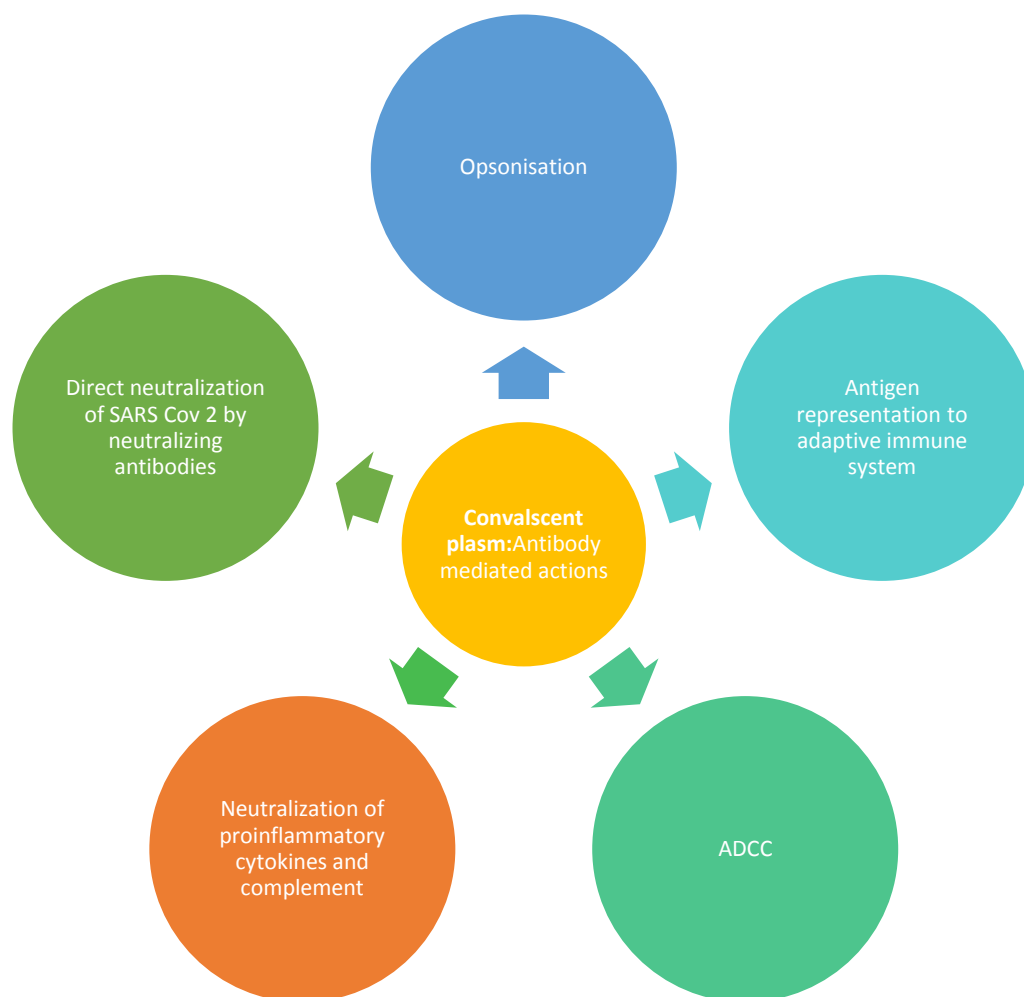
entry into the host cells, enhance the viral clearance through antibody mediated cellular toxicity. Table 1 Hence its most efficacious when used in the early viremia phase of illness, majority of patients achieve seroconversion within two weeks of symptom onset [19-24]. While data regarding the long-term duration of this humoral response in COVID-19 are still evolving, studies conducted during the SARS epidemic have shown that this antibody response is short- lasting, with peak levels at around 3-4 months followed by gradual waning over the next two years [25].

The protective index of plasma can be directly assessed by the neutralizing activity, which has been used as a gold standard for the quantification of its efficacy. These are functional assays which involve incubating serial dilutions of the plasma with a standard dose of the live virus and inoculation of this mixture in a culture medium. The fraction of dilution of the plasma that prevents the culture of the virus or its cytopathic effect is defined as the neutralizing titre of the plasma [26]. However, these assays are not available on a large scale for CP therapy because of accessibility and standardization problems. The Fig. (2) depicts the possible post-

donation modifications to CP to create safer, more potent, standardized passive immunization products such as hyper immune globulins and monoclonal antibodies against SARS-CoV-2.

Commercially available serological assays as alternatives to neutralizing assays is an attractive option. A few recent publications have demonstrated a good correlation of several such serological titres, especially assays targeting the S-RBD Blood Centre (NYBC) found that two commercial domain and neutralizing assays [26-33]. The New York assays (by Abbott and ORTHOS) showed a good correlation with N Ab titres in a study of serum from 370 CP donors [16]. The Con COVID group investigators from the Netherlands found a good correlation of a commercially available ELISA with neutralization assays [13]. The assay manufactured by Euro Immune AG has also been shown to correlate with neutralization assays [17] and used in a RCT from Spain [19]. Another issue in the antibody titre measurement of CP is the wide variability in the methodology and cut-offs used in the literature. Ideally, these parameters need to be standardized and validated in clinical trials before clinical use but for the need of the hour we had to forgo these measures.

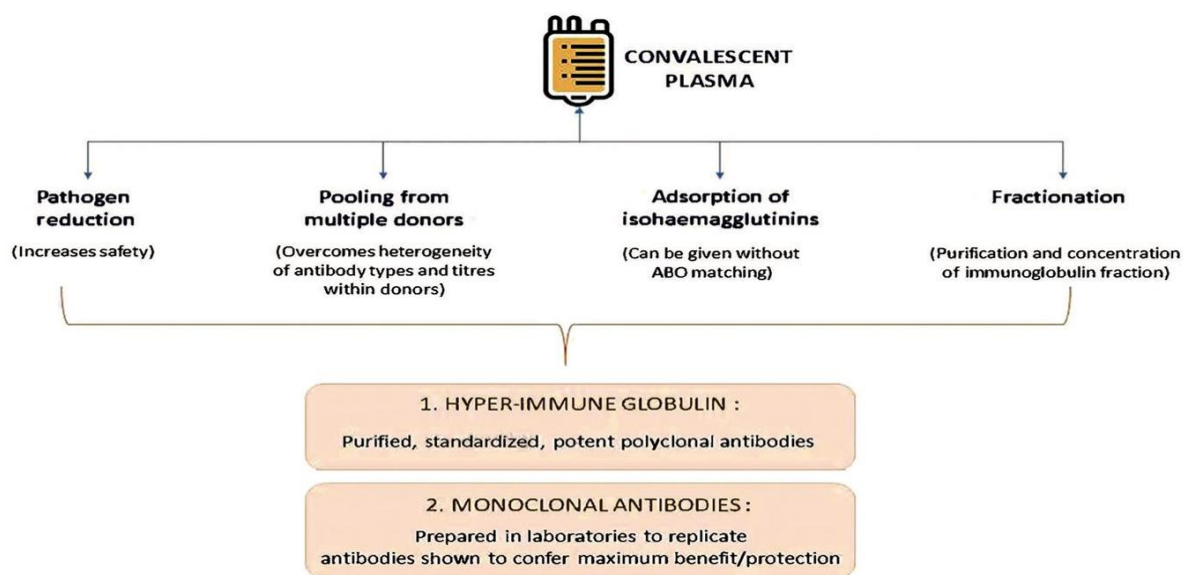




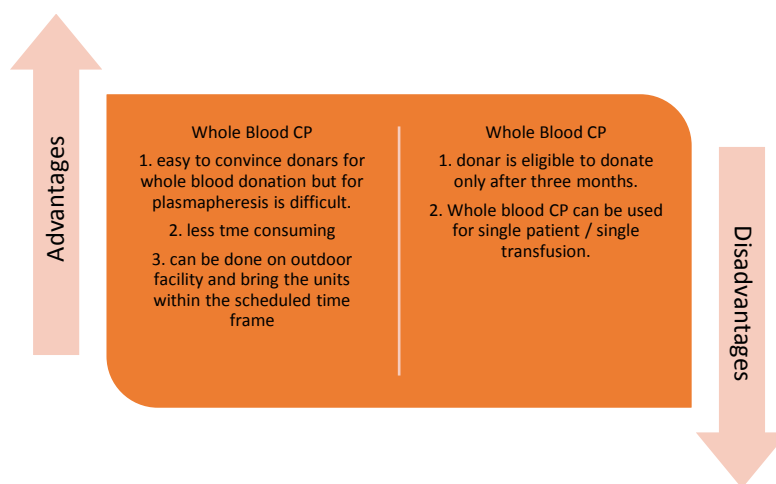
**Fig. 1. Mechanisms of actions on the basis of antibody and non-antibody mediated of Convalescent Plasma (a & b)**

**Table 1. Suitability of convalescent plasma (CP) use during outbreaks by novel pathogens**

Rapidity of deployment	CP can be put to clinical use as soon as a pool of individuals recovered from the illness is available
Ease of production and use	Plasma collection and infusion are relatively straightforward and commonly performed procedures. Most healthcare workers will be familiar with the procedure and will require no extra training. In resource-constraint settings, convalescent whole blood can also be used instead of plasma
Accessibility	The expertise and equipment to perform plasmapheresis, storage and deployment are commonly available in most tertiary care centres around the globe
Specificity	The CP, by its very nature, is specific against the targeted infectious agent. In a few instances, such as the 1918 Spanish flu, CP was used even before the identification of the pathogenic agent. The use of CP locally will help prepare a product with specific action against the particular antigenic variant prevalent in that particular geographical area
Immediate onset of action	Helps confer immediate protection to individuals already suffering from the disease
Safety	Risks of CP infusion are minimal, and it is a safe therapy
Scalability	Can be easily scaled up to the level of a large population



**Fig. 2. Post-donation modifications of convalescent plasma (CP)**



**Fig. 3. The advantages and disadvantages of Whole Blood Convalescent Plasma**

#### 4. WHO ARE THE DONORS

Healthy adults who have recently recovered from COVID 19 and remained asymptomatic for minimum 14 days are potential CP donors for COVID-19. This period is assessed on the basic estimates of antibody kinetics and period of infectivity. Documented nasopharyngeal swab PCR negativity before CP donation is no longer mandatory in most CP protocols across the globe [23]. Based on the available antibody kinetics data, the ideal window for donation is 3-4 months after symptom onset [32]. There is a wide variability in the titres of anti- SARS-CoV-2 antibodies within donors [24]. Initial data from China showed that a high proportion of donors (39/40) possessed N Ab titres >1:160 [25].

However, recent reports have shown more variations. In the NYBC report, 55% of the screened 370 CP donors did not have high titre antibodies, while 10% had very high levels [16]. The Con COVID group reported similar findings in a cohort of 115 plasma donors, with 43% screened donors having neutralizing titres >1:320 and 10% with titres >1:1280 [17]. In other studies, the proportion of donors found lacking in high titre antibodies ranged from 25 to 50%, with about 10-20% having very high antibody levels of more than 20 times the cut-off limits, the so-called “super-donor phenotype” [26,34,35]. Older age, male gender and clinical features such as moderate-to-severe disease, [30] high C-reactive protein (CRP) and lymphocytopenia have been found to be associated with higher N

Ab titres [26,36]. Notably, asymptomatic individuals have been found to mount a very transient and low titre antibody response [33]. These clinical and demographic factors may help to guide the selection of suitable donors. The compassionate use programmes in the USA and Israel followed this approach and determined antibody titres of the infused plasma units *post hoc*, and their findings have been recently published [18,37]. The Indian Council of Medical Research (ICMR)-sponsored PLACID trial also followed this strategy [38]. The antibody titres in this study were found to be low, with a median neutralization titre of 1:40 [interquartile range (IQR) 1:30-1:80] [39]. These findings have highlighted the hazards of proceeding with CP therapy without appropriate antibody quantification in real time. For now, it seems to be a reasonable strategy to screen potential CP donors for the presence of anti- SARS-CoV-2 antibodies using commercially available serological tests to exclude donors with low anti-SARS-CoV-2 antibodies.

## 5. WHO ARE THE RECIPIENTS

Patients who have been confirmed by RTPCR test to be suffering from COVID 19 and are critically ill. They have to be treated at a designated COVID 19 management set up. Vaccination status may/ may not be considered.

## 6. PLASMA COLLECTION, DOSAGE AND MODE OF ADMINISTRATION

A prospective donor should fulfil the standard donor screening criteria, as per the Drugs and Cosmetics Rules, 1945 [40]. and the COVID-19 advisory from National Blood Transfusion Council (NBTC) [41]. This should be emphasised that plasma donation is a voluntary exercise and requires informed permission. Although whole blood can be used in resource-limited settings, plasmapheresis remains the preferred method of CP donation because of the larger collection volume of plasma, the feasibility of repeated collections and the minimal impact on the donor's haemoglobin. Up to 15 per cent of total blood volume (400-800 ml per session) can be safely donated in a single sitting [42-45]. Recommendations allow for serial plasma donations by a single donor with a minimum gap of seven days between consecutive plasmapheresis sessions [44,45]. Donated plasma is frozen at less than  $-30^{\circ}\text{C}$  (preferably  $-40$  to  $-80^{\circ}\text{C}$ ) within 8-24 h of collection and can be stored for up to 12 months. Pathogen

inactivation by techniques such as photochemical inactivation or solvent detergent treatment and pooling from multiple donors are other post-donation processing options to improve the safety and quality. With this procedure about 400 ml of plasma is obtained from donor's body which can be divided into two aliquots of 200 ml of each (One dose = 200 ml of plasma transfusion). The dosage of administration would be 200 ml over 2 hrs and can be repeated after 24 hrs. This collected plasma can be stored frozen at  $-40^{\circ}\text{C}$ , if required and thawed before transfusion. The donor can again donate at an interval of 14 days. The plasma which is transfused should be ABO compatible [46-49,26,50]

## 7. WHEN IS THE BEST TIME TO PRESCRIBE CP TO COVID-19 PATIENTS?

The use of CP is best illustrated at four clinical levels i.e. Post exposure prophylaxis, asymptomatic to mild illness, moderate to severe illness and critically ill. It seems that CP is highly recommended to be given in the first week of infection (viremia stage) and early in the course [27]. The assumed mechanism of action of CP is such that it prevents or delays the establishment of infection long enough to allow the host immune response to acknowledge and clear the infection. In addition, treatment with CP therapy could decrease serum cytokine production, decreased mortality rates, and lower down viral load of H5N1 influenza virus, in the respiratory system of patients in the first week of infection. However, SARS patients develop deadly immune responses represented by cytokine storms during the second week of infection [28]. Later stages of illness the hyper inflammatory state is the major cause for mortality. To add, the ongoing tissue damage helps maintain the inflammatory state as a vicious cycle and in this control on viral replication may have a minimal effect on disease course. In general, it sounds that the best time to give CP therapy to SARS patients during early stages of infection. Therefore, and based on previous data, it is recommended to give CP therapy in the early stages for COVID-19 patients [27,28,33,51,52].

## 8. SAFETY CONCERNS WITH CP THERAPY

Common reactions encountered are transfusion reactions, antibody mediated enhancements and attenuation of antibody response. The

transfusion reactions have remarkably reduced, due to constant ABO compatibility and HLA screening. In the study conducted in a group of 20,000, the risk of reactions that were transfusion related, thromboembolic and cardiac events were recorded less than 1% [53]. Other safety analyses before CP injection includes analyses of blood type, antibody of the species, virus-immunofluorescence analysis for detection of hepatitis C and B diseases, HIV, and syphilis and detection of DNA viruses by RT PCR. With the use of guideline based screening strategies, it carries a nonzero risk of transfusion associated infections. Other complications include allergic reactions, TRALI and TACO. COVID 19 cases with already compromised respiratory efficiency may specially be vulnerable to TRALI/ TACO which may be difficult to differentiate with the progress of disease. CP efficiency analyses and measurements of the proportion of antibody to the "COVID-19" virus are also to be carried out, and the efficacy of those antibodies against the virus needs to be checked, a phenomenon usually seen in viral infections like dengue [53-58]. It is proposed that these pre-existing antibodies are sub neutralizing in nature and mask the viral epitopes from any immune recognition, in turn facilitating intracellular entry and survival, leading to worsening of the disease. Although no studies have proven this so far in COVID 19.

## **9. IDENTIFYING CONVALESCENT PLASMA**

While detecting COVID 19, SI RBD Ig G, plasma was labelled as  $\alpha\beta$ - CP, when titres were above the cut off values. Depending on the institution the cut off values were defined according to the kit being used and that's how their own SOPs were made. However, plasma which showed results below the cut off value was not considered for treatment and was sent for fractionation.

The procedure of apheresis to whole blood convalescent plasma has its own advantages (Fig 3):

- Plasma collection using apheresis facility is ideal because it optimizes efficiency and frequency of collection.
- Some donors were also interested to donate because they wanted to store their COVID Ig G rich plasma for their own future use in case requirement

arises during the other phases of the pandemic.

## **10. HOW DOES IT DIFFER FROM VACCINATION**

There are two forms of immunity active and passive. Active antibodies are the ones that develop in an individual's own immune system after the body is exposed to an antigen through a disease or when we get an immunization or vaccine shot. This takes time to develop but lasts for long. On the contrast passive immunity comprises of the preformed antibodies given to a person to prevent disease or to treat disease after the body is exposed to an antigen. This form of immunity lasts only for a few weeks or months. So basically vaccination is active immunity but convalescent plasma therapy is passive immunity [29-32,59].

## **11. HOW DO WE MEASURE THE EFFICACY OF CONVALESCENT PLASMA THERAPY (CPT)**

To understand the efficacy of CPT, two issues need to be addressed primarily. Firstly, how long do these antibodies remain at high levels to continue providing therapeutic effects. Secondly, are multiple transfusions necessary during the patient's disease course and recovery. A multicentre, randomized controlled trial conducted in 39 tertiary care hospitals across India. Four hundred and sixty-four adults with moderate COVID-19 infection were enrolled, out of which 235 received CPT and best standard of care (intervention arm) and 229 were randomized to receive best standard of care only (control arm). This study found no conclusive difference in 28-day mortality or progression to severe disease among patients with moderate COVID-19 treated with convalescent plasma along with best standard of care. Additional, outcomes did not differ between participants receiving convalescent plasma with detectable neutralizing antibody titres compared with participants receiving best standard of care alone; or between those receiving convalescent plasma with neutralizing antibody titres of 1:80 or higher and those receiving best standard of care alone. Limitations of this study were, that the median day of enrolment from symptom onset was eight days and 83% of the trial participants had detectable neutralizing antibodies at the time of enrolment itself. In Wuhan, another open label multicentre, randomized clinical trial was

performed in seven medical centres and they studied the effect of CPT with standard treatment and compared with standard treatment alone, on the clinical presentation in patients with severe and life threatening COVID 19. The authors concluded that convalescent plasma therapy added to standard treatment did not result in any significant improvement in severe or life threatening COVID 19 cases within the span of 28 days but further conclusions could not be drawn as the study had an early termination [60].

## 12. WHAT WAS THE PROBLEM

In the Indian set up, the main handicap of limited access to apheresis facility since very few blood banks have apheresis facilities. Inadequate infrastructure adds to the problem. Manpower and technical expertise are also at shortage to perform plasmapheresis since it's a specialized procedure but this did not stop us from doing what's to be done. Plasma can be collected in set ups which do not have apheresis facilities since it can be separated from a random donation of whole blood unit from a recovered patient. This can be done with the help of cryo-centrifuge easily in whole blood collected in double bags, but the plasma separated would amount to 200-220 ml, i.e. only one dose of CP. Moreover, a whole blood donation would also cause loss of RBCs from a donor as a result of which he /she can donate again only after 90/120 days depending on the gender of the donor. However, this method was not recommended by ICMR in its approval protocol. Other than the infrastructural issues, we have seen several variants of COVID 19, with different antigenic characteristics, manifestations, an inadequate protection by the vaccination and also failure of neutralization by antisera. The numerous variants are likely to make CPT ineffective specially if derived from patients who have recovered from older strains.

## 13. CONVALESCENT PLASMA THERAPY INDIAN SCENARIO

The efficacy of usage of CP is still debatable in India, though if proven it will be beneficial in treatment of COVID 19. In channel to this, effort will have to be made to make antibody testing available before any large scale implementation is done. To bring this to effect PLACID trial was done which has been published, this included PLATINA which was an open label RCT of CP use in severe COVID 19 cases in 21 centres across Maharashtra [60]. The Director General

of Health Services (DGHS), Government of India, in its letter dated 14<sup>th</sup> April 2020 has given permission to ICMR to use convalescent plasma therapy as part of a two arm multicentre phase II randomized control trial [61]. Hence ICMR based on applications received, permitted five states viz. Delhi, Punjab, Gujrat, Karnataka and Kerala to start the trial in initial phase. The primary objective being to assess the efficacy of CP to limit complications in COVID 19 patients, also to evaluate the safety of treatment with this regime [61].

Another operational requirement, the handicap of which was felt, the CP units should be available to the patients as soon as possible, ideally targeting within three days of diagnosis. The scarcity of donors added to the problem. The concept of voluntary blood donation has always been a handicap in India [62]. Apart from the social barriers like lockdowns and curfews, there were psychological blocks too like reluctance to donate including fear of visiting a health care facility during an epidemic, waning of immunity and risk of reinfection due to CP donation, to name a few. Creating awareness and stockpile good enough to cater large population, provide prophylaxis for health care workers and enough raw material for producing purified products in the future requires major health for all goals. Motivating donors for plasmapheresis without fear is necessary to overcome these shortages.

The Drug Controller General of India has approved the drug to be administered only under a trial protocol. The Ministry of Health and Family Welfare (MoHFW) guidelines for the treatment of COVID-19 lists CP as an off-label experimental therapy option. These guidelines recommend using CP after the measurement of antibody titres by neutralization assays or anti-S-RBD IgG ELISA, which may not be possible in most centres of the country. For the design of clinical and research protocols guidelines issued by global regulatory bodies such as WHO [63]. International Society of Blood Transfusion (ISBT). USFDA and European Commission may be useful.

In the month of May 2021, we dropped the convalescent plasma therapy from its national clinical management protocol for COVID 19. The decision was taken by the AIIMS ICMR COVID 19 National Task Force and the Health Ministry indicated that CP offered no therapeutic benefits in patients admitted to hospital with the disease. It came three days after findings of the recovery



trial, the largest randomized trial to report results of the effect of convalescent plasma in patients hospitalized with COVID 19 was published in Lancet [41].

#### 14. CAN WE STILL COUNT ON CPT IN TREATMENT OF COVID 19

In the initial period of illness, when the patients progress from mild to moderate disease and are likely to develop complications, CPT with antiviral medications can delay such an occurrence. The administration of steroids can be delayed up to the beginning of second week of illness, even if the patient is under hypoxia. The newer variants of the virus will keep emerging and the CP obtained from recently recovered COVID 19 subjects is likely to provide the best protection with neutralizing antibodies against the newer variants [64-66]. The studies have proven that criticality of when was CP therapy done in the course of disease is significant. The administration of CCP with high antibody titres to at risk patient early i.e. Within seven days of the onset of illness appears a safe and sound modality to curb the disease progression. The rampant usage of steroids as the magic treatment in the early progression of the disease has given way to delayed use of CPT in second week with severe disease and probably ongoing viral replication [67-69].

#### 15. CONCLUSION

Convalescent plasma may be promising, feasible and safe treatment option for COVID 19 but its usage is limited to those with early disease, in patients at risk for developing a severe illness and in those showing early signs of worsening disease. In Indian setting its efficacy remains to be unequivocally established. Further research on donor selection, antibody cut offs, precise indications of use and dosing is required before more widespread CP usage becomes possible. Emerging evidence points out the necessity of measuring antibody titre in infused plasma units and care should be taken to infuse only high titre CPT from recently recovered individuals from COVID 19. The routine non pharmaceutical interventions like face masks, social distancing and person hygiene along with the vaccination drives will for now remain the key to managing and preventing future outbreaks. The development of more potent modalities such as hyper immune globulins would be the next step

in enhancing passive immune transfer based therapeutic for COVID 19.

#### CONSENT

It is not applicable.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

#### REFERENCE

1. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Hu Y. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proceedings of the National Academy of Sciences*, 2020; 117(17):9490-9496.
2. Tiberghien P, de Lamballerie, X, Morel, P, Gallian, P, Lacombe, K, Y Azdanpanah, Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how? *VoxSanguinis*, 2020;115(6):488-494.
3. Zeng Q-L, Yu Z-J., Gou J-J, Li G-M., Ma S-H., Zhang G-F, Zhang M-M. Effect of convalescent plasma therapy on viral shedding and survival in COVID-19 patients. *The Journal of Infectious Diseases*, 2020;1(1):38-43.
4. Zhang B, Liu S, Tan T, Huang W, Dong, Y., Chen, L, Zhang X. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest*, 2020;158(1):e9-e13.
5. Zhai, P, Ding, Y, Wu X, Long, J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *International Journal of Antimicrobial Agents*, 2020; 55(5):105955.
6. Working Party of Global Blood Safety, International Society of Blood Transfusion. Points to Consider in the Preparation and Transfusion of COVID-19 Convalescent Plasma in Low-and Middle-Income Countries. Available:[http://isbtweb.org/fileadmin/user\\_upload/FINAL\\_Points\\_to\\_consider\\_in\\_the\\_preparation\\_of\\_COVID\\_convalescent\\_plasma\\_in\\_LMIC.pdf](http://isbtweb.org/fileadmin/user_upload/FINAL_Points_to_consider_in_the_preparation_of_COVID_convalescent_plasma_in_LMIC.pdf), accessed on May 9, 2020.

7. Anonymous Monograph on the epidemic of poliomyelitis (infantile paralysis) in New York City in 1916. New York City Department of Health, New York, 1917 (cited by Wyatt HV. Before the vaccines: medical treatments of acute paralysis in the 1916 New York epidemic of poliomyelitis. *Open Microbiol J.* 2014; 8:144–7.
8. Hess AF. A protective therapy for mumps. *Am J Dis Child.* 1915; 310:99–103.
9. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med.* 2006;145(8):599–609.
10. Nicolle C, Conseil E. Pouvoir preventif du serum d'un malade convalescent de rougeole. *Bul Soc Méd Hôp Paris.* 1918; 42:336–8.
11. Van Griensven, J, Edwards, T, de Lamballerie X, Semple, MG, Gallian P, Baize S, Antierens A. Evaluation of convalescent plasma for Ebola virus disease in Guinea. *New England Journal of Medicine,* 2016;374(1):33-42.
12. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest* 2020; 130: 2757-65.
13. Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in COVID-19: Possible mechanisms of action. *Autoimmun Rev* 2020; 19: 102554.
14. Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liunbruno GM, et al. Convalescent plasma: New evidence for an old therapeutic tool? *Blood Transfus* 2016; 14: 152-7.
15. Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA.* 2020;324(5):460–470. doi:10.1001/jama.2020.10044
16. Siracusano G, Pastori C, Lopalco L. Humoral immune responses in COVID-19 patients: A window on the state of the art. *Front Immunol* 2020; 11: 1049.
17. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579: 270-3.
18. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. *Emerg Microbes Infect* 2020; 9:382-5.
19. Wu F WA, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv; 2020. doi: 10.1101/2020033020047365.
20. Okba NM, Müller MA, Li W, Wang C, GeurtsvanKessel CH, Corman VM, et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease patients. *Emerg Infect Dis* 2020; 26: 1478-88.
21. Suthar MS, Zimmerman MG, Kauffman RC, Mantus G, Linderman SL, Hudson WH, et al. Rapid generation of neutralizing antibody responses in COVID-19 patients. *Cell Rep Med* 2020;1: 100040.
22. Prompetchara E, Ketloy C, Palaga T. Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 2020; 38: 1-9.
23. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis* 2020; 28: ciaa344.
24. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, et al. Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). *Clin Infect Dis* 2020; 71: 778-85.
25. Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, Baril L, et al. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *J Infect Dis* 2006; 193:792-5.
26. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Lv T. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *Journal of Medical Virology,* 2020;92(10):1890-1901.
27. Hung IF, To KK, Lee C-K, Lee K-L, Chan K, Yan W-W, Lai K-Y. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clinical Infectious Diseases,* 2011;52(4):447-456.
28. Cheng Y, Wong R, Soo Y, Wong W, Lee C, Ng M, Cheng G. Use of convalescent plasma therapy in SARS patients in Hong

- Kong. *European Journal of Clinical Microbiology and Infectious Diseases*, 2005;24(1):44-46.
29. Marano G, Vaglio S, Pupell S, Facco G, Catalano L, Liembruno, GM, Grazzini, G. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfusion*, 2016;14(2):152.
  30. Roback JD, Guarner J. Convalescent plasma to treat COVID- 19: possibilities and challenges. *JAMA*, 2020;323(16):1561-1562.
  31. Zhao Q, He Y. Challenges of convalescent plasma therapy on COVID-19. *Journal of Clinical Virology*, 2020;127:104358.
  32. WHO. Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks. Version 1.0; 2014. Available:[https://apps.who.int/iris/bitstream/handle/10665/135591/WHO\\_HIS\\_SDS\\_2014.8\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/135591/WHO_HIS_SDS_2014.8_eng.pdf). Accessed 15June 2021.
  33. Hartman W, Hess AS, Connor JP. Hospitalized COVID-19 patients treated with convalescent plasma in a mid-size city in the Midwest. *medRxiv*; 2020. doi: 10.1101/2020.06.19.20135830.
  34. Rajendran K, Krishnasamy N, Rangarajan J, Rathinam J, Natarajan M, Ramachandran A. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. *J Med Virol* 2020;92:1475-83.
  35. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Rahman F, et al. Convalescent plasma treatment of severe COVID-19: A propensity score-matched control study. *Nat Med* 2020; 26: 1708-13.
  36. Perotti C, Baldanti F, Bruno R, Fante CD, Seminari E, Casari S, et al. Mortality reduction in 46 severe COVID-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter trial. *Haematologica* 2020; 105: 2834-40.
  37. Rasheed AM, Fatak DF, Hashim HA, Maulood MF, Kabah KK, Almusawi YA, et al. The therapeutic potential of convalescent plasma therapy on treating critically-ill COVID-19 patients residing in respiratory care units in hospitals in Baghdad, Iraq. *Infez Med* 2020;28: 357-66.
  38. Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, and Quek SC. The many estimates of the COVID-19 case fatality rate. *Lancet Infect Dis*. 2020.
  39. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses? *Microbes Infect* 2020; 22: 72-3.
  40. Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* 2020; 95: 1888-97.
  41. National AIDS Control Organisation, Ministry of Health and Family Welfare, Government of India. Volume of plasma, Plasmapheresis, Apheresis. Standards for Blood banks and Blood Transfusion Services. Available:[http://nbtc.naco.gov.in/assets/resources/sop/Standards\\_for\\_Blood\\_Banks\\_and\\_Blood\\_Transfusion\\_Services.pdf](http://nbtc.naco.gov.in/assets/resources/sop/Standards_for_Blood_Banks_and_Blood_Transfusion_Services.pdf), accessed on October 18, 2020.
  42. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. *Chest* 2020; 158: e9-13.
  43. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *J Korean Med Sci* 2020; 35: e149.
  44. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol* 2020; 92: 1890-1901.
  45. Zeng QL, Yu ZJ, Gou JJ, Li GM, Ma SH, Zhang GF, et al. Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019. *J Infect Dis* 2020;222:38-43
  46. Hoffbrand AV, Higgs, DR, Keeling DM, Mehta AB. *Postgraduate Haematology*: John Wiley & Sons; 2016.
  47. Burnouf, T, Radosevich M. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Medical Journal*,2003; 9(4):309.
  48. Cheng, Y., Wong, R., Soo, Y., Wong, W., Lee, C., Ng, M. and Cheng, G. (2005). Use of convalescent plasma therapy in SARS patients in Hong Kong. *European Journal of Clinical Microbiology and Infectious Diseases*, 24(1), 44-46.
  49. Wong HK, Lee, CK, Hung IF, Leung JN, Hong J, Yuen KY, Lin CK. Practical limitations of convalescent plasma collection: a case scenario in pandemic

- preparation for influenza A (H1N1) infection. *Transfusion*, 2010; 50(9):1967-1971.
50. Klassen SA, Senefeld JW, Senese KA, Johnson PW, Wiggins CC, Baker SE, van Helmond N, Bruno KA, Pirofski L-a, Shoham S, Grossman BJ, Henderson JP, Wright RS, Fairweather D, Paneth NS, Carter RE, Casadevall A, Joyner MJ. Convalescent Plasma Therapy for COVID-19: A Graphical Mosaic of the Worldwide Evidence. *Front. Med.* 2021;8:684151. DOI: 10.3389/fmed.2021.684151
  51. Ministry of Health and Family Welfare, Government of India. Drugs and Cosmetics Act 1940 and Rules 1945, Amended. Available: [https://cdsco.gov.in/opencms/export/sites/CDSCO\\_WEB/Pdf documents/acts rules/2016DrugsandCosmeticsAct1940Rules1945.pdf](https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf documents/acts rules/2016DrugsandCosmeticsAct1940Rules1945.pdf), accessed on October 18, 2020.
  52. Szakó L, Farkas N, Kiss S, et al. Convalescent plasma therapy for COVID-19 patients: a protocol of a prospective meta-analysis of randomized controlled trials. *Trials.* 2021;22:112 Available: <https://doi.org/10.1186/s13063-021-05066-2>
  53. Pontecorvo M. Ciba Geigy Edizioni; Origgio: 1991. Storia delle vaccinazioni: dalle origini ai giorni nostri; p. 104.
  54. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases*, 2020;20(4)(4):398-400.
  55. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Hu Y. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proceedings of the National Academy of Sciences*, 2020;117(17):9490-9496.
  56. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, Zhang X. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest*, 2020;158(1):e9-e13.
  57. National Blood Transfusion Council. Guidelines for Blood Donor selection and Blood Donor Referral. Available: <http://nbtco.naco.gov.in/assets/resources/policy/Letter-reg-%20guidelines-for-blood-donor-selection&referral-2017.pdf>, accessed on October 18, 2020.
  58. WHO Blood Regulators Network (2017) Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus; 2020. Available: [https://www.who.int/bloodproducts/brn/2017\\_BRN\\_PositionPaper\\_ConvalescentPlasma.pdf?ua=1](https://www.who.int/bloodproducts/brn/2017_BRN_PositionPaper_ConvalescentPlasma.pdf?ua=1), accessed on October 18, 2020.
  59. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases*, 2020;20(4)(4):398-400.
  60. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). *BMJ.* 2020;371:m3939.
  61. Epstein J, Burnouf T. Points to consider in the preparation and transfusion of COVID-19 convalescent plasma. *Vox Sang* 2020; 115: 485-7.
  62. Marwaha N. Voluntary blood donation in India: Achievements, expectations and challenges. *Asian J Transfusion Sci* 2015; 9: S1-2.
  63. National Institutes of Health. Llama Antibody Engineered to Block Coronavirus; 2020. Available: <https://www.nih.gov/news-events/nih-research-matters/llama-antibody-engineered-block-coronavirus>, accessed on October 18, 2020
  64. Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee Guidelines for the Blood Transfusion Services 3.7: Volume of Donation. Available: <https://www.transfusionguidelines.org/red-book/chapter-3-care-and-selection-of-whole-blood-and-component-donors-including-donors-of-pre-deposit-autologous-blood/3-7-volume-of-donation>, accessed on October 18, 2020.
  65. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. *J Clin Invest* 2020; 130: 4791-7.

66. Ministry of Health and Family Welfare, Government of India. Clinical Management Protocol: COVID-19. Available: [https://www.mohfw.gov.in/pdf/ClinicalManagement Protocol for COVID19.pdf](https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19.pdf), accessed on October 18, 2020.
67. Nobel Lectures, Physiology or Medicine 1901-1921, Elsevier Publishing Company, Amsterdam; 1967.
68. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. *Science* 2017; 358: 929-32.
69. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020; 323: 1582-9.

---

© 2021 Vimal et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*Peer-review history:*

*The peer review history for this paper can be accessed here:*  
<https://www.sdiarticle4.com/review-history/74533>