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Convalescent (Immune) Plasma Therapy with all Aspects: Yesterday, Today and COVID-19

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ABSTRACT

At the end of 2019, the pandemic, which originated in China, has become a major concern all over the world. A new coronavirus, severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), has been defined as the reason for a cluster of unknown pneumonia. Thus far, no precise therapy or vaccine has been shown to be effective against SARS-CoV-2 infection. Mild cases can be treated by supportive care although symptomatic treatment is not enough for critically ill patients. However, extracorporeal membrane oxygenation, convalescent (immune) plasma (CIP) and certain specific antiviral drugs for this disease are still being investigated for improving the survival rate of cases with SARS-CoV-2 infection whose condition continued to deteriorate. The use of passive immunization, for the prophylaxis and therapy of human contagious diseases, has been gone back to the 20th century. Human whole blood is also a source of antibodies. CIP consists of collecting blood plasma from someone who has recovered from a specific infection. Recent literature data show that human CIP may be an alternative option for managing coronavirus disease 2019 (COVID-19) and will be accessible when adequate numbers of individuals have improved. However, such donors should have a high titer of neutralizing immunoglobulin-containing plasma. CIP can be administered to improve the survival rate for COVID-19, together with other drugs and preventive measures, when specific management is not obtainable. On the other hand, randomized clinical trials are still necessary to assess the safety and efficiency of CIP in the therapy of COVID-19. In this article, we want to address the special role of CIP therapy in various infectious diseases from yesterday to today, including COVID-19.

Keywords: COVID-19, SARS-CoV-2, convalescent immune plasma

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INTRODUCTION

As of 31 December 2020, the World Health Organization (WHO) was informed on the first patient with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1). The current approach to clinical management of SARS-CoV-2 infection mostly focuses on general supportive care. Beyond supportive care, there are currently no proven therapeutic options for pneumonia of coronavirus disease 2019 (COVID-19), taken place by SARS-CoV-2 infection. Human convalescent (immune) plasma (CIP) administration could be a choice for treatment of COVID-19 and will be accessible when satisfactory numbers of individuals improved (2–4). Finding some therapeutic CIP trials as beneficial has led to FDA approval to treat critically ill COVID-19 patients for wider use (2).

Passive antibody therapy has been tracing back to the 1890s and was the only way of managing several contagious diseases before the advancement of antimicrobial treatment in the 1940s. Before the 1940s, passive antibody (serum) administration was helpful in the management of various contagious diseases (4). However, antibiotic chemotherapy was later observed to be more effective and less toxic than antibody therapy. In the 21st century, the efficiency of antimicrobials is plummeting due to the quickly increasing number of immunocompromised individuals, the appearance of novel pathogens, the return of old pathogens, and the widespread increase of resistance to antimicrobial medications (5).

In this paper, we want to cover the special role of CIP therapy in various infectious diseases from yesterday to today, including COVID-19. In the preparation of this manuscript, PubMed, Web of Science Core Collection (Clarivate), Scopus, WHO, CDC, ECDC, and the web addresses of clinical trials (www.clinicaltrials.gov) and Turkish Ministry of Health (www.saglik.gov.tr) searched by the keywords (COVID-19, SARS-CoV-2, CIP). The clinical studies, meta-analysis and review papers released in the last six months' (from November 2019 to April 2020) collection for the preparation of the manuscript were reviewed and evaluated for this narrative review.

What is Convalescent (Immune) Plasma?

As a form of passive antibody therapy, CIP therapy is a form of passive immunization. To produce CIP, the liquid

component (plasma) of whole blood should be taken from someone who has survived a SARS-CoV-2 or similar infection. However, many new treatment protocols mention CIP as a therapy of last resort. We think that this might be a defensive approach owing to the inadequate clinical experience of CIP administration into this severely ill patient group (2, 3).

CIP can immediately provide neutralizing antibodies against the viral pathogens in COVID-19 susceptible or infected patients for the prevention or treatment of contagious disease, but the immunoglobulins will last only for a short time, weeks to possibly a few months. On the contrary, active vaccination involves the stimulation of an immune system reaction that passes time to build up a response varying among recipients; even some immunocompromised patients may fail to achieve an adequate immune response. Thus, passive antibody use is the only way of providing instant immunity to vulnerable people and immunity of any measurable kind for highly immunocompromised patients.

Historic Clinical Trials

While every viral disease and epidemic is different, historical samples (Table 1) provide important knowledge for both comforting and being helpful as humanity fights with the COVID-19 pandemic (6–9).

Management of influenza cases with the pneumonia complication by the utilization of convalescent serum was begun at U. S. Naval Hospital on September 28, 1918. Convalescent blood products used to treat 1703 patients with Spanish influenza pneumonia between 1918 and 1925. Cases with Spanish influenza pneumonia that had influenza-convalescent human blood products caused a clinically significant decline in the risk of fatality (10). Each donor yielded about 300 ml of serum at a time on two successive days. The most beneficial results will be achieved by administering the appropriate serum within the first 48 hours of the pneumonia complication. The serum therapy was shortened the course of the disease and decreased the fatality (11). The absolute decrease in the risk of fatality varied from 18.66% to 21.60% in different studies (6).

At the beginning of the 20th century, convalescent sera were utilized to stop epidemics of viral diseases (e.g., measles and mumps) (7, 8). Also, serum treatment was used as intra-spinal and subcutaneously in some patients of epidemic poliomyelitis (12).

Management of severe H1N1 2009 infection with CIP treatment decreased airway viral load, serum cytokine levels (interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)- α), and mortality (13). The mean duration of hospital admission was shorter after therapy. Reductions in the ICU duration, mechanical ventilation, and ECMO were reported. No adverse events or complications were described after CIP therapy (6).

In avian influenza A (H5N1), trivial benefits subsequent to CIP administration were demonstrated. However, data were not decisive (6).

Convalescent blood product was also utilized in the 2013 West African Ebola epidemic. A small nonrandomized study in Sierra Leone showed notably longer survival for those given convalescent whole blood, compared to patients who take regular management (9). Also, there are some reports about the efficiency of CIP therapy

Table 1. Historical use of convalescent (immune) blood product (serum/plasma) therapies to treat various infectious diseases (6–8, 15)

Spanish influenza A (H1N1)	Poliomyelitis
Avian influenza A (H5N1)	Meningitis
MERS-CoV infection	Pneumococcal pneumonia
SARS coronavirus (SARS-CoV)	2013 West African Ebola epidemic
Hepatitis	2009 pandemic influenza A (H1N1) (influenza A [H1N1] pdm09)
Rabies	Mumps and measles

for SARS in 2003 and Middle East respiratory syndrome (MERS) in 2012. In these epidemics, high fatality and lack of proven therapeutics led to the utilization of convalescent serum. Derived from samples of the past literature, CIP transfusion was considered for the treatment of MERS-CoV infection and was essentially utilized in several cases during the 2015 Korean epidemic (14).

A meta-analysis of 32 trials of SARS-CoV infection and severe influenza demonstrated a statistically significant decline in the pooled odds of fatality after CIP therapy concerning placebo or no therapy (odds ratio: 0.25; 95% CI, 0.14–0.45). In SARS-CoV infection, the absolute decrease in the risk of death varied from 7% to 23% (95% CI, 5.59–42.02) in two studies. Subgroup assessments indicated that early therapy was more valuable. Discharge from the hospital by day 22 was 54% higher after CIP management (77% vs. 23%) (6).

In conclusion, more than the last two decades, convalescent whole blood product therapy has been utilized (Table 2) in the therapy of SARS, MERS, and 2009 influenza A H1N1 pandemic (H1N1pdm09) with adequate efficacy and safety (10, 13, 14). However, the convalescent whole blood therapy was unable to considerably advance the survival of the Ebola virus disease, probably attributable to the lack of data of neutralizing antibody titration for graded evaluation (9, 14). Since the virological and clinical features having resemblance among SARS, MERS, and COVID-19 diseases, CIP therapy could be a hopeful therapeutic alternative for COVID-19 recovery.

Current Clinical Experiences in COVID-19

Shen et al. reported case series of five critically ill COVID-19 patients who were administered CIP transfusion with a SARS-CoV-2-specific antibody (IgG) binding titer higher than 1:1000 and a neutralization titer more than 1:40. CIP was utilized between the 10th and 22nd days of hospitalization. In addition, the patients' neutralizing antibody titers increased and respiratory samples tested negative for SARS-CoV-2 between the 1st and 12th days after transfusion (15).

In another study, four seriously ill cases with SARS-CoV-2 infection were given palliative management and different amounts of CIP at various time points. All four cases were in ARDS clinic, were also taken antiviral therapy and, two of them required ECMO support. Among four cases, who given CIP, the time from the CIP transfusion to negative RT-PCR test varied from 3 to 22 days. The third and fourth cases developed anti-SARS-CoV-2 IgG roughly on the 14th day of CIP infusion. ARDS improved in four patients on

Table 2. Administration of the convalescent (immune) plasma therapy in coronavirus epidemics

Disease	Dose (volume) of CIP	Antibody titers	Summarized findings
SARS (28, 37, 41–43)	-279±127 (160–640) ml	Not stated	• Overall, 80 cases received CIP. 10 patients died.
	-500 mL	Antibody (IgG) titer: >640	CIP at ~14 (7–30) days following the onset of symptoms
	-200 ml	Not stated	Good clinical outcome in 33 patients as defined by hospital discharge by day 22
	-2 units of 250 mL each (total 500 mL)	Not stated	Improved outcome with early administration No adverse events
MERS (26, 37, 44, 45)	-4 transfusions of CIP to 3 patients; volumes not stated	1:40 or 1:80	• Questionable benefit even though all 3 patients survived
	-2 units (250–350 mL/unit)	Not stated	• Feasibility study to evaluate the ratio of convalescent donors having antibodies against MERS-CoV
	-250 mL	Not stated	• Case report of 1 patient Possible TRALI observed
COVID-19 (15, 17, 37)	-200 mL	Neutralizing antibody titer: >1:640	• Uncontrolled 10 severely ill patients CIP at 16.5 (11.0–19.3) days Recovery of all patients No significant adverse effect
	-2 consecutive transfusions of 200–250 mL (400 mL total)	ELISA Anti-SARS-CoV-2- antibody titer : >1:1000 Neutralizing antibody titer: >1:40	• Uncontrolled 5 critically ill cases CIP at 10–22 days after admission Recovery of all patients

the 12th day of infusion, and two cases were weaned from mechanical ventilation within two weeks. Of the five cases, three have been discharged, and two patients were in stable condition at 37th day of transfusion (16). Randomized clinical trials are required to deduct the result of other therapeutic methods and explore the real safety and efficacy of CIP infusion.

In China, CIP therapy was administered into 245 COVID-19 patients, and 91 cases have shown improvement in clinical indicators and symptoms day by day (17).

In a different clinical trial, SARS-CoV-2 ribonucleic acid negativity was detected after CIP transfusion in all enrolled cases. One unit of CIP with high titers of neutralizing antibodies swiftly diminished the viral load and inclined to ameliorate clinical manifestations. Only once, 200 ml CIP gathered from lately recuperated donors with the neutralizing antibody titers above 1:640 was infused to the cases as a supportive to maximal palliative care and antiviral drugs. The clinical symptoms and lymphocyte counts were significantly got better in conjunction with raise in oxyhemoglobin saturation within three days and absorption of lung lesions in chest scans in seven days, without any adverse effects (18).

Effect Mechanisms of Convalescent (Immune) Plasma Therapy

The polyclonality of neutralizing antibodies in CIP would diminish the risk of a runaway mutant, which is more probable to appear in cases managed with the monoclonal antibody. The effects of CIP may be rather instant in finishing the infective course and lessening the cytokine storm. Adamantines and neuraminidase inhibitors or even newer antivirals effective against the viral ribonucleoprotein cannot inactivate any viruses that have already penetrated the host cells (19). Polyclonal antibody from CIP, may have a role to hinder SARS-CoV-2 spike glycoprotein (S)- related entry into cells and limit viral replication.

Known antiviral medications thwart either viral dismantling after entrance or viral expel from host cells. Although it is uncertain how CIP transfusion ameliorates the COVID-19 patients' clinical manifestations, the neutralizing and non-neutralizing antibodies might also ease viral entry into Fc-receptor-bearing antigen-presenting cells (e.g., macrophages and B lymphocytes). Since these cells are commonly not tolerant to the expansion of influenza virus (20), augmented viral uptake is improbable to endanger cell function but may actually enhance viral antigen processing and presentation to

boost T lymphocyte-mediated adaptive immune responses (21). Also, the antibodies from CIP may suppress viremia in this way.

Plasma components in CIP can also provide benefits in critically ill patients. There are beneficial effects, such as replenishing coagulation factors, when given to patients with hemorrhagic fevers, such as Ebola (22). On the other hand, CIP preparations involve mostly disease-specific IgG antibodies in standardized doses. There is not any IgM titer, which may be necessary against some viruses. However, whether other supportive treatments, including antivirals, steroids, and intravenous immunoglobulin, have any effects on the relationship between CIP and its antibody level or not is unknown.

Timing and Quantity (the dose) of Convalescent (Immune) Plasma Infusion

Despite the potential utility of passive antibody treatments, there have been few concerted efforts to use them as initial therapies against emerging and pandemic infectious threats. As there are few studies, it contributed to the hesitancy to employ this treatment. Also, the most effective formulations (convalescent whole blood, serum or plasma), timing and quantity of administration are unknown.

Depend on the antibody quantity and ingredient, the protection period provided by CIP can prolong from weeks to months. For effective therapy, a sufficient amount of CIP must be administered at the exact time. Time is very important because CIP will travel in the blood, contact tissues, and offer defense against the infection in time.

Serial of 173 plasma samples gathered during the admission were checked for total antibodies, IgM and IgG against SARS-CoV-2. Among 173 cases, the seroconversion rate for total antibodies, IgM and IgG was 93.1% (161/173), 82.7% (143/173) and 64.7% (112/173), respectively. The seroconversion consecutively detected for total antibodies, IgM and then, IgG, with a median time of 11, 12 and 14 days, respectively. The existence of antibodies was <40% among cases in the first seven days of the disease and then quickly increased to 100.0%, 94.3% and 79.8% for total antibodies, IgM and IgG, respectively, since day 15 after disease onset. On the contrary, the positivity of SARS-CoV-2 ribonucleic acid declined from 66.7% (58/87) in specimens obtained before day 7 to 45.5% (25/55) during days 15 to 39. Additionally, a higher titer of total antibodies was separately linked with a poorer clinical categorization (23).

As there is no proven evidence about elimination time of antibodies to SARS-CoV-2 from serum; Cao et al. demonstrated that the level of specific neutralizing antibody to SARS-CoV diminished slowly four months past the disease course, achieving unnoticeable IgG levels in 25.6% and neutralizing antibodies in 16.1% of cases at three years following disease recuperation (24).

Passive antibody treatment for pneumococcal pneumonia was most successful when applied immediately following the start of manifestations, and there was no profit if treatment was deferred after the third day of disease onset (25).

Individual convalescent plasma units demonstrate donor-dependent variability in antibody specificities and titers. MERS-CoV-infected cases without pneumonia showed a 60% seroconversion

rate, while 96% of pneumonia cases demonstrated seroconversion. This distinction in seroconversion rate indicates that donors should be checked for antibody titers, otherwise be preferred from cases who recuperated from severe/critical illness (26). For a successful CIP infusion in MERS-CoV infection, testing donor plasma for antibody and neutralization activity of a PRNT (plaque reduction neutralization test) titer $\geq 1:80$ might be required. Controlling IgG titers by ELISA could replace for neutralization tests in limited availability (27).

An analysis of 99 specimens of convalescent sera from cases with SARS demonstrated that 87 had neutralizing antibody, with a geometric mean titer of 1:61 (28). During the 2003 SARS outbreak, outcomes of patients who received CIP in Hong Kong were reported. There were 1775 patients, the 80 who received CIP had a lower fatality rate (12.5%) compared with the overall SARS-related mortality for admitted patients (17%). The antibody titers and plasma transfusion volumes varied and did not appear to correlate with the clinical response; however, patients receiving transfusion within 14 days of symptom onset (n: 33) had better outcomes (29).

Zhang and et al. reported four critically ill patients with SARS-CoV-2 using CIP therapy around two weeks of hospitalization. Depend on the patient, 200 to 2400 ml was used to recover from COVID-19 (16). Tiberghien et al. advocated the infusion of two plasma units of 200 to 250 ml each in cases at the day 5th of treatment weighing between 50 and 80 kg, volume to be accustomed for cases weighing outside this limit (30).

In a study, 10 seriously ill COVID-19 cases enrolled and one unit of 200 mL of CIP with the neutralizing antibody titers above 1:640 was infused as support to maximal palliative care and antiviral agents. The median time from the start of illness to CIP infusion was 16.5 days. The clinical manifestations were significantly recuperated in the company with an increment of oxyhemoglobin saturation within three days, yielding to the vanishing of viremia in seven days. In the meantime, clinical features and paraclinical markers quickly ameliorated within three days. Several parameters inclined to ameliorate as matched up to pretransfusion, comprising raised lymphocyte numbers ($0.65 \times 10^9/L$ vs. $0.76 \times 10^9/L$) and diminished C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiology demonstrated changing degrees of resolution of pulmonary lesions within seven days. The viral load was untraceable after infusion in seven cases. No severe adverse effects were reported and well-tolerated. CIP therapy potentially improves the clinical characteristics by way of neutralizing viremia in severe COVID-19 cases (31).

In the ongoing randomized controlled clinical trials, 1 unit is planned for preventive use and 1–2 units are suggested for therapeutic use. The preferred dosing was based on earlier knowledge of CIP therapy in SARS, where 5 mL/kg of plasma at an antibody titer of 1:160 was given (29).

In brief, nobody knows that exactly what dose and in which time CIP therapy would be most effective. Even manufacturing highly purified preparations comprising of a high titer of neutralizing antibodies, hyperimmune globulin, against SARS2-CoV-2 may be desirable than CIP, given that they are safer and have higher activity. Also amount of antibodies administered probably changes for different conditions

Table 3. Requirements for the donor and recipient eligibility of convalescent (immune) plasma therapy treatment (2, 18, 34, 35, 46)

Donor eligibility	Patient eligibility
COVID-19 disease documented by a laboratory test, including swab/RT-PCR.	Laboratory confirmed COVID-19 disease (real-time RT-PCR assay). Severe or immediately life-threatening disease:
Complete resolution of symptoms at least 14 days before donation.	Severe disease signs; one or more of the following <ul style="list-style-type: none"> - shortness of breath (dyspnea), - respiratory frequency ≥ 30/min, - oxygen saturation $\leq 93\%$ - the partial pressure of arterial oxygen (PaO₂)/inspired oxygen ratio (FiO₂) <300 mmHg - lung infiltrates >50% within 24 to 48 hours
Negative test (swab/RT-PCR) results for COVID-19 disease.	<i>Administration on the 7–14th day of infection is recommended.</i>
Male donors or female donors who have not been pregnant or female donors who have been tested as negative for HLA antibodies to exclude TRALI.	<i>Oxygen saturation level <90% while administrating 5L/min and more O₂ support by nasal canula.</i>
Defined SARS-CoV-2 neutralizing antibody titers. Neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.	<i>Rapid progression of illness condition and poor prognostic parameters (lymphopenia, the elevation of CRP, ESR, ferritin, LDH, D-dimer).</i>
<i>Donated plasma should compatible with the A-B-O blood type of the recipient.</i>	<i>Need for vasopressor and /or mechanical ventilation.</i>
<i>Negative indirect Coombs test.</i>	<i>Negative screening for immunoglobulin A deficiency.</i>
<i>Age ≥ 18 years</i>	<i>Age ≥ 18 years</i>

Requirements in italics: distinct/additional requirements according to the Turkish Ministry of Health

(e.g., prophylaxis or treatment). More than 10 clinical trials of CIP infusion in COVID-19 patients are currently ongoing to detect timing and quantity (the dose) of administration (<http://www.chictr.org.cn/> and <https://clinicaltrials.gov/>. As of March 15, 2020).

Better for Post-exposure Prophylaxis or Therapy?

A common opinion of passive antibody treatment is that it is more helpful when utilized for prevention than management. When administered for treatment, the antibody is most successful when administered abruptly after the start of clinical manifestations. The temporal disparity in efficiency is not well-known but could reveal that passive antibody functions by neutralizing the preliminary inoculum, which is possible to be much lesser than that of established disease (32). Another clarification is that passive antibody performs by adjusting the inflammatory response, which is also more sim-

ply accomplished during the early immune response, a phase that might be asymptomatic (33).

In prophylactic use, convalescent serum administration can avoid infection and following an illness in those who are at high risk for disease, e.g., cases with predisposing medical conditions, health care professionals, and those who closely contacted with verified COVID-19 cases. This is just like passive antibody administration for hepatitis B, rabies and respiratory syncytial virus immune globulin to prevent these diseases.

Patient Eligibility

In the first plan, CIP therapy would be administered in any case with severe or immediately critical of laboratory-verified COVID-19 cases (Table 3). Severe illness signs comprise dyspnea, breathing

frequency ≥ 30 /min, oxygen saturation $\leq 93\%$, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , and pulmonary infiltrates $> 50\%$ in 24–48 hours. Critical illness characteristics contain breathing failure, septic shock and multi-organ failure (2).

Donor Eligibility for Convalescent (Immune) Plasma Transfusion

In a study, 10 donor patients who recuperated from COVID-19 were enrolled from three contributing hospitals. The donor's whole blood was gathered three weeks after the start of illness and four days after discharge. Written informed consent should be acquired from each donor. In the beginning, the serological scanning for hepatitis B and C virus, human immunodeficiency virus, and syphilis and SARS-CoV-2 and RT-PCR test should be done (18, 34).

Titration of antibodies is helpful before the use of CIP for prevention or treatment. COVID-19 patients generated SARS-CoV-2-specific and spike-binding antibodies concurrently from day 10 to 15 after infection. About 30% of recovered patients generated very low titers of SARS-CoV-2-specific antibodies. Elderly and middle-age recovered COVID-19 patients developed higher levels of SARS-CoV-2-specific antibodies. COVID-19 recovered cases' age and SARS-CoV-2-specific antibody titers negatively correlated with lymphocyte count and positively correlated with CRP levels on admission. These all data above can guide which donor is more beneficial for CIP compilation (35).

In brief, CIP must only be gathered from people who convene all blood/plasma donor eligibility, as well as the following requirements (Table 3). i-) Individuals have confirmation of COVID-19 recognized by a laboratory test, including swab/RT-PCR. ii-) Complete improvement of manifestations at least 14 days before donation, and negative test (swab/ RT-PCR) results for COVID-19. iii-) Male donors or female donors who are not pregnant or female donors checked as negative for HLA antibodies to exclude transfusion-related acute lung injury (TRALI). iv-) SARS-CoV-2 neutralizing antibody titers of at least 1:160. A titer of 1:80 may be thought to be acceptable if a different appropriate unit is not existing (2).

Adverse Effects of CIP Transfusion

Minor reactions

- Transfusion-like reactions arise from the unpredictable reactivity against the blood product used (serum, plasma, or whole blood), e.g., a transient elevation in body temperature by 0.5–1.5°C 30 to 120 minutes after the transfusion. In a CIP trial for Ebola disease in 2015, no severe adverse effects were observed in 99 patients. Minor adverse effects were detected in 9% of the cases, frequently fever (5%) and/or itching or cutaneous rash (4%) (30). If the transfusion is too fast, increased side effects may be seen in critically ill cases.
- Hyperpyrexia shortly after transfusion
- Phlebitis and generalized jaundice

Moderate to serious transfusion-related adverse events

- Reactions to serum ingredients (involving immunological reactions, e.g., serum sickness.)
- Anaphylaxis

- Transmission of the potential pathogen (another infectious disease agent)
- When CIP therapy administered into cases with pulmonary involvement, plasma transfusion brings some risk for the development of TRALI (36). After apheresis, there should also be obligatory testing of female donors having a pregnancy history for HLA antibodies to lessen the risk of TRALI (2). Particularly, two cases of possible TRALI after CIP have been described in a case with Ebola disease and case with MERS-CoV infection. In both cases, infused CIP was detected to be a lack of anti-HLA or anti-HNA antibody (30).
- Transfusion-associated circulatory overload (TACO) in specifically patients with cardio-respiratory disease, advanced age and renal impairment (37).
- Antibody-dependent enhancement of infection (ADEI) is a theoretical concern for SARS-CoV-2 infection. ADEI is common in vitro cell cultures using monoclonal antibodies but rarely occurs in vivo except for dengue virus. ADEI can take place in many viral diseases and exacerbate disease in the existence of certain antibodies. For coronaviruses, quite a few explanations for ADEI have been described, and there is the hypothetical worry that antibodies to one type of coronavirus could boost the infective process to another viral strain. Rather comforting is an obvious lack of ADEI information with the use of CIP in SARS, MERS or COVID-19 diseases (37, 38).

It is indefinite to what degree CIP might diminish the progress of an expected immune response, in particular when applied for prevention.

Should CIP Recipient be Vaccinated for SARS-CoV-2 When the Vaccine is Developed?

Antibody administration to SARS-CoV-2 infected patients may thwart disease by attenuating the immune response, putting such cases at risk for the following reinfection. By the way, passive antibody therapy ahead of vaccination with RSV was demonstrated to alleviate humoral but not cellular immunity (39). Because of this worry, the patients who administered CIP therapy should be examined by measuring immune responses. If the risk proves to be true, these cases ought to be immunized to COVID-19 when a vaccine will be obtainable.

Can Transferred Maternal Humoral Immune Response Act like a CIP therapy?

In a study, six pregnant women with confirmed COVID-19 and their newborns were examined in detail for the detection of infection. All of the newborns have negative results for quantitative RT-PCR for SARS-CoV-2 ribonucleic acid. All six infants had antibodies detected in their serum. Two infants had IgG and IgM concentrations higher than the normal level (< 10 AU/mL). Three infants had elevated IgG but normal IgM levels. Inflammatory cytokine IL-6 was significantly increased in all infants. One infant and his mother had low IgG and Ig M levels. None of the infants presented any symptoms. IgG is usually passively transferred across from mother placenta to the fetus, but IgM, which has a larger macromolecular structure, cannot pass through. Alternatively, IgM could have been produced by the infant if the virus crossed the placenta. This data suggest that the transmitted virus could be neu-

tralized by IgG and then possibly IgM, consequently resulting in negative PCR tests in infants (40).

CONCLUSION

Deploying passive antibody therapies, such as CIP for the COVID-19, immediately can be a life-saving strategy. In this condition, assessing clinical studies on the efficacy of this treatment against a viral agent should be increased. For more CIP, blood centers should start collecting plasma from convalescing donors. Clinicians can encourage COVID-19–infected patients in visits to donating plasma after hospital discharge. If the results of large-scale randomized clinical trials demonstrate efficacy, the use of this therapy also could help change the course of this pandemic. The optimum dose and application period of CIP therapy still will require more investigation in the near future.

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REFERENCES

- World Health Organization (WHO). Novel coronavirus - China. Available from: URL: <https://www.who.int/csr/don/12-january-2020-novel-coronavirus-china/en/>. Accessed, January 12, 2020.
- FDA. Recommendations for Investigational COVID-19 Convalescent Plasma. Available from: URL: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma>.
- WHO MERS-CoV Research Group. State of Knowledge and Data Gaps of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Humans. *PLoS Curr* 2013; 5: ecurrents.outbreaks.0bf719e352e7478f8ad85fa30127ddb8.
- Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. *Lancet Infect Dis* 2020; 20(4): 398–400. [CrossRef]
- Casadevall A, Scharff MD. Return to the past: the case for antibody-based therapies in infectious diseases. *Clin Infect Dis* 1995; 21(1): 150–61. [CrossRef]
- Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, et al. Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015; 211(1): 80–90. [CrossRef]
- Gallagher JR. Use of Convalescent Measles Serum to Control Measles in a Preparatory School. *Am J Public Health Nations Health* 1935; 25(5): 595–8. [CrossRef]
- Rambar AC. Mumps; use of convalescent serum in the treatment and prophylaxis of orchitis. *Am J Dis Child* 1946; 71: 1–13. [CrossRef]
- Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. *J Infect* 2017; 74(3): 302–9. [CrossRef]
- 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. [CrossRef]
- Mcguire LW, Redden WR. The use of convalescent human serum in influenza pneumonia—a preliminary report. *Am J Public Health (N Y)* 1918; 8(10): 741–4. [CrossRef]
- Amoss HL, Chesney AM. A Report on the Serum Treatment of Twenty-Six Cases Of Epidemic Poliomyelitis. *J Exp Med* 1917; 25(4): 581–608. [CrossRef]
- Hung IF, To KK, Lee CK, Lee KL, Chan K, Yan WW, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011; 52(4): 447–56. [CrossRef]
- Mustafa S, Balkhy H, Gabere MN. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review. *J Infect Public Health* 2018; 11(1): 9–17. [CrossRef]
- Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of critically ill patients with COVID-19 with convalescent plasma. *JAMA*. Available from: URL: <https://jamanetwork.com/journals/jama/fullarticle/2763983>. Accessed, March 27, 2020. [CrossRef]
- Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. *Chest*. 2020 Mar 31:S0012-3692(20)30571-7. doi: 10.1016/j.chest.2020.03.039. [Epub ahead of print] [CrossRef]
- China puts 245 COVID-19 patients on convalescent plasma therapy. News release. Xinhua. February 28, 2020. Available from: URL: http://www.xinhuanet.com/english/2020-02/28/c_138828177.htm. Accessed, March 10, 2020.
- Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. Available from: URL: <https://www.medrxiv.org/content/10.1101/2020.03.16.20036145v1.full.pdf+html>. Accessed March 23, 2020.
- Kao RY, Yang D, Lau LS, Tsui WH, Hu L, Dai J, et al. Identification of influenza A nucleoprotein as an antiviral target. *Nat Biotechnol* 2010; 28(6): 600–5. [CrossRef]
- Wells MA, Albrecht P, Daniel S, Ennis FA. Host defense mechanisms against influenza virus: interaction of influenza virus with murine macrophages in vitro. *Infect Immun* 1978; 22(3): 758–62. [CrossRef]
- Magro M, Andreu D, Gómez-Puertas P, Melero JA, Palomo C. Neutralization of human respiratory syncytial virus infectivity by antibodies and low-molecular-weight compounds targeted against the fusion glycoprotein. *J Virol* 2010; 84(16): 7970–82. [CrossRef]
- Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020; 130(4): 1545–8. [CrossRef]
- 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 Mar 28:ciaa344. doi: 10.1093/cid/ciaa344. [Epub ahead of print] [CrossRef]
- Cao WC, Liu W, Zhang PH, Zhang F, Richardus JH. Disappearance of antibodies to SARS-associated coronavirus after recovery. *N Engl J Med* 2007; 357(11): 1162–3. [CrossRef]
- Casadevall A, Scharff MD. Serum therapy revisited: animal models of infection and development of passive antibody therapy. *Antimicrob Agents Chemother* 1994; 38(8): 1695–702. [CrossRef]
- Ko JH, Müller MA, Seok H, Park GE, Lee JY, Cho SY, et al. Serologic responses of 42 MERS-coronavirus-infected patients according to the disease severity. *Diagn Microbiol Infect Dis* 2017; 89(2): 106–11. [CrossRef]
- Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. *Antivir Ther* 2018;

- 23(7): 617–22. [CrossRef]
28. Zhang JS, Chen JT, Liu YX, Zhang ZS, Gao H, Liu Y, et al. A serological survey on neutralizing antibody titer of SARS convalescent sera. *J Med Virol* 2005; 77(2): 147–50. [CrossRef]
29. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005; 24(1): 44–6. [CrossRef]
30. Tiberghien P, de Lamballerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how. *Vox Sang*. 2020 Apr 2. doi: 10.1111/vox.12926. [Epub ahead of print] [CrossRef]
31. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *Proc Natl Acad Sci U S A*. 2020 Apr 6:202004168. doi: 10.1073/pnas.2004168117. [Epub ahead of print] [CrossRef]
32. Robbins JB, Schneerson R, Szu SC. Perspective: hypothesis: serum IgG antibody is sufficient to confer protection against infectious diseases by inactivating the inoculum. *J Infect Dis* 1995; 171(6): 1387–98. [CrossRef]
33. Casadevall A, Pirofski LA. Antibody-mediated regulation of cellular immunity and the inflammatory response. *Trends Immunol* 2003; 24(9): 474–8. [CrossRef]
34. The Mayo Clinic IRB. Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19. Available from: URL: <https://www.uscovidplasma.org/pdf/COVID-19%20Plasma%20EAP.pdf>. Accessed April 5, 2020.
35. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia J, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implication. Available from: URL: <https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v1.full.pdf>. Accessed April 6, 2020. [CrossRef]
36. Gajic O, Rana R, Winters JL, Yilmaz M, Mendez JL, Rickman OB, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. *Am J Respir Crit Care Med* 2007; 176(9): 886–91. [CrossRef]
37. 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 Apr 7:138745. doi: 10.1172/JCI138745. [Epub ahead of print] [CrossRef]
38. Tetro JA. Is COVID-19 receiving ADE from other coronaviruses?. *Microbes Infect* 2020; 22(2): 72–3. [CrossRef]
39. Crowe JE Jr, Firestone CY, Murphy BR. Passively acquired antibodies suppress humoral but not cell-mediated immunity in mice immunized with live attenuated respiratory syncytial virus vaccines. *J Immunol* 2001; 167(7): 3910–8. [CrossRef]
40. Zeng H, Xu C, Fan J, Tang Y, Deng Q, Zhang W, et al. Antibodies in Infants Born to Mothers With COVID-19 Pneumonia. *JAMA*. 2020 Mar 26:e204861. doi: 10.1001/jama.2020.4861. [Epub ahead of print] [CrossRef]
41. Yeh KM, Chiueh TS, Siu LK, Lin JC, Chan PK, Peng MY, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. *J Antimicrob Chemother* 2005; 56(5): 919–22. [CrossRef]
42. Wong VW, Dai D, Wu AK, Sung JJ. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J* 2003; 9(3): 199–201.
43. Kong L. Severe acute respiratory syndrome (SARS). *Transfus Apher Sci* 2003; 29(1): 101. [CrossRef]
44. Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, et al. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. *Emerg Infect Dis* 2016; 22(9): 1554–61. [CrossRef]
45. Chun S, Chung CR, Ha YE, Han TH, Ki CS, Kang ES, et al. Possible Transfusion-Related Acute Lung Injury Following Convalescent Plasma Transfusion in a Patient With Middle East Respiratory Syndrome. *Ann Lab Med* 2016; 36(4): 393–5. [CrossRef]
46. Turkish Ministry of Health Immune Plasma Guidelines, 2020. Available from: URL: https://dosyamerkez.saglik.gov.tr/Eklenti/37163,covid-19-immun-plazma-rehberi-12-nisan-2020-sonv1-ti-neopdfpdf.pdf?0&_tag1=D61DB6867EF68EE9A7FE73C870D9BBA04AACCC05C.