

## **Clinical Investigator's Brochure for Use of Convalescent Plasma to Treat Coronavirus-19 (COVID-19) Disease**

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### List of Abbreviations

AABB	American Association of Blood Banks
Anti-HBc	Hepatitis B core antibodies
ARDS	Acute Respiratory Distress Syndrome
BMT	Bone marrow transplant
CMV	Cytomegalovirus
COVID-19	Coronavirus Infectious Disease -19 (novel coronavirus) disease caused by SARS-CoV-2 virus
CCP	COVID-19 Convalescent Plasma
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
HBsAg	Surface antigen of the hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-cell lymphotropic virus
ICU	Intensive Care Unit
IVIG	Intravenous immune globulin
MERS	Middle East Respiratory Syndrome
NAT	Nucleic acid testing
RSV	Respiratory syncytial virus
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19
TACO	Transfusion-associated circulatory overload
TRALI	Transfusion related acute lung injury
WHO	World Health Organization

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## **2 Summary**

This information brochure has been developed specifically for use with the Expanded Access Program (EAP) under IND 19832. The information contained within the document is being provided to participating treating physicians along with the protocol and consent form to assist in protecting the patients being treated as part of this EAP.

This expanded access program will provide access to investigational COVID-19 convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who have severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Following registration on the protocol and provision of informed consent, patients will be transfused with convalescent plasma obtained from an individual who has recovered from documented infection with SARS-CoV-2. Safety information collected will include serious adverse events. Other information to be collected retrospectively will include patient demographics, acute care facility resource utilization (total length of stay, days in ICU, days intubated, and survival to discharge from an acute care facility).

Plasma has been and is being collected by registered or licensed blood banks, including the American Red Cross. Collection of plasma will be done using the guidelines from AABB, the FDA, and the American Red Cross or as contained in the COVID-19 Convalescent Plasma Collection Protocol, and using otherwise standard operating procedures at the blood establishments.

Plasma from patients who have recovered from a documented SARS-CoV-2 infection may contain high titer anti-SARS CoV-2 antibodies which may be able to modify the course of the infection and decrease morbidity and mortality associated with SARS-CoV-2 infection when transfused into hospitalized patients in a serious or life-threatening situation or at high risk for progression of severe disease.

### 3 Introduction

#### Background <sup>[6]</sup>

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.<sup>1</sup> In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV epidemic.

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials.

FDA guidance (<https://www.fda.gov/media/136798/download>) provides recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. FDA guidance also provides recommendations to blood establishments on the collection of COVID-19 convalescent plasma.

Severe morbidity and mortality is occurring during this COVID-19 Pandemic. Since there is no currently recognized effective standard of care treatment for patients infected with SARS-CoV-2, multiple investigational agents are being tested. These include antivirals marketed or approved for other indications or being developed specifically for SARS-Co V-2 and other immunotherapies.

Convalescent plasma has appeared to be of benefit for the treatment of certain infectious diseases, including infections from respiratory viruses. Preliminary evidence indicates that convalescent plasma may possibly be of benefit for some patients with COVID-19, leading to improvement.

The collection and transfusion of convalescent plasma as a treatment was first used in the 1890s and helped reduce the severity of a number of infectious disease outbreaks prior to the development of antimicrobial therapy in the 1940s.

In the early 20th century, convalescent plasma treatment was used during outbreaks of various infectious diseases, including measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic in 2009, and again in 2013 during the Ebola outbreak in West Africa.

One of the ways that people fight off infectious diseases is by developing antibodies that lead to the destruction of the invading microorganism. The antibodies are present in the blood, and more specifically in the liquid portion of the blood called plasma. People who have recovered from being recently infected can donate plasma and that plasma can then be given to individuals who are ill with the virus in order to try to help eliminate it from the system and allow them to get better. This has worked in previous outbreaks of respiratory diseases like influenza, and there are some early data to suggest that it might work for some people with COVID-19.<sup>[1-3]</sup>

The FDA is permitting the use of convalescent plasma as an investigational treatment for patients with moderate or severe COVID-19 infection. It is considered an investigational treatment because clinical studies have started but have not yet been completed. We know there is evidence that convalescent plasma has helped patients with other illnesses, but doctors and researchers will not know how effective convalescent plasma will be in treating COVID-19 patients until more studies are completed.

While additional treatment options are evolving, convalescent plasma can be considered and may help some moderately or severely ill patients. The idea to use this treatment for the new coronavirus was suggested by Arturo Casadevall, MD, PhD, from Johns Hopkins University; and Liise-anne Pirofski, MD, from the Albert Einstein College of Medicine.<sup>[4]</sup>

## **4 Physical, Chemical and Pharmaceutical Properties and Formulation.**

The product to be administered is COVID-19 Convalescent Plasma. This is human plasma, collected from patients who have recovered from a documented infection with the novel coronavirus, SARS-CoV-2 who have been screened for blood borne pathogens, according to standard FDA criteria to be qualified as plasma/blood donors.

### **4.1 Donor Qualifications**

COVID-19 convalescent plasma must only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15). Required testing must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

#### **Plasma Donations from Recovered COVID-19 Patients**<sup>[5,6]</sup>

The American Red Cross and other organizations are seeking people who are fully recovered from COVID-19 and may be able to donate plasma to help current patients with serious or immediately life-threatening COVID-19 infections, or those judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. Donor qualifications will be assessed based on the current guidelines at the time of donation.

5. American Red Cross – Plasma Donations from Recovered COVID-19 Patients  
<https://www.redcrossblood.org/donate-blood/dlp/plasma-donations-from-recovered-covid-19-patients.html> (Accessed 6/5/2020)
6. Investigational COVID-19 Convalescent Plasma – Guidance for Industry (April 2020, Updated May 1, 2020)  
<https://www.fda.gov/media/136798/download> (Accessed 6/5/2020)

People who have fully recovered from COVID-19 have antibodies in their plasma that can attack the virus. This convalescent plasma is being evaluated as treatment for patients seriously ill with COVID-19. Historically, convalescent plasma has been used as a potentially lifesaving treatment when new diseases or infections develop quickly, and no treatments or vaccines were available yet. The American Red Cross and other organizations have been asked by the U.S. Food and Drug Administration (FDA) to help identify prospective donors and manage the distribution of these products to hospitals treating patients in need.

The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6 (a))

All units of plasma have been collected at registered or licensed blood banks and in accordance with the blood bank SOPs for a plasma product. Units of plasma will have been stored at the collection site or a central repository prior to shipping to the sites participating in the Expanded Access Program.

All plasma collected for use under this Expanded Access Program will have the following characteristics:

- Negative Anti-HIV-1/2
- Negative Anti-HTLV-I/II
- Negative Anti-HCV
- Negative HBsAg
- Negative for anti-HBc
- Negative serologic test for syphilis
- Negative anti-*T. cruzi* or history of a negative test if a previous blood donor
- Negative testing for Babesia or a history of a negative test for Babesia, depending upon geographic residency of the donor. (Note: This testing is required in beginning May 4, 2020. Residents of endemic areas are tested with each donation.)
- Negative West Nile Virus (WNV) NAT
- Negative HCV NAT
- Negative HIV NAT
- Negative HBV NAT
- Negative Zika NAT

In the event of new infectious diseases that are potentially transmitted by blood products, all plasma collected under this Expanded Access Program will follow FDA guidance regarding the screening of donors and/or additional serologic or nucleic acid testing (NAT). All plasma products will be labeled in a manner to allow traceability for the purpose of infectious disease testing, identification and if necessary recipient notification.

## 4.2 Convalescent Plasma Preparation

This Expanded Access Program will make available COVID-19 Convalescent Plasma collected by registered or licensed blood establishments in accordance with the AABB Circular of Information<sup>[29]</sup> the American Red Cross – Plasma Donations from Recovered COVID-19 Patients<sup>[5]</sup> and FDA's regulations and the additional Investigational COVID-19 Convalescent Plasma – Guidance for Industry<sup>[6]</sup>



### **4.3 Convalescent Plasma Administration**

Before administration of the COVID-19 convalescent plasma the treating clinician must have registered as a site, as a physician and have registered the patient in the EAP. The treating clinician or designee must document properly obtained informed consent, read through the protocol and appropriately direct the use of the convalescent plasma. The physician or designee must check the label to verify that the information on the label as it relates to the transfusion to the intended patient is correct.

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution's guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

COVID-19 Convalescent Plasma will be administered according to standard hospital procedures.

The infusion can occur through a peripheral or central venous catheter and will be given according to standard institutional medical and nursing practices for the administration of plasma.

Initial data available from studies using COVID-19 convalescent plasma for the treatment of individuals with severe or life-threatening disease indicate that a single dose of 200 mL showed potential efficacy.

The volume of plasma to be transfused should be based upon the patient's weight and clinical comorbidities (e.g. patients with impaired cardiac function and heart failure may require less volume or more prolonged transfusion times). The volume of plasma to be transfused should be at least one unit (approximately 200 mL) but may be greater if the treating clinician concludes a larger volume is appropriate. Transfusions may occur at any time throughout the hospitalization including multiple doses on non-sequential days. In general, it is expected that most patients will receive two units or less, but this language is not intended to restrict the use of convalescent plasma in larger quantities when the treating physician determines that such volumes and/or re-treatment are clinically justified.

COVID-19 Convalescent Plasma will be supplied as an investigational blood product for the treatment of COVID-19.

## 5 Preclinical Development

COVID-19 Convalescent Plasma has not undergone any preclinical evaluation.

## 6 Previous Human Experience

### 6.1 Use in COVID-19

#### **Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients**<sup>[42]</sup>

Joyner MJ et al., Mayo Clinic Proceedings Pre-print June 2020

[https://els-jbs-prod-cdn.jbs.elsevierhealth.com/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp\\_ft95\\_6\\_8.pdf](https://els-jbs-prod-cdn.jbs.elsevierhealth.com/pb/assets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf)

**Objective:** To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized COVID-19 patients, having previously demonstrated safety in 5,000 hospitalized patients.

**Patients and Methods:** From April 3 to June 2, 2020, the US FDA Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma.

**Results:** The incidence of all serious adverse events was low; these included transfusion reactions ( $n=89$ ;  $<1\%$ ), thromboembolic or thrombotic events ( $n=87$ ;  $<1\%$ ), and cardiac events ( $n=680$ ,  $\sim 3\%$ ). Notably, the vast majority of the thromboembolic or thrombotic events ( $n=55$ ) and cardiac events ( $n=562$ ) were judged to be unrelated to the plasma transfusion *per se*. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

**Conclusion:** These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

**Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients** <sup>[2]</sup>  
Joyner MJ et al., May 2020, doi: <https://doi.org/10.1101/2020.05.12.20099879>

- Mayo Clinic and collaborators reported safety data on the first 5,000 hospitalized patients transfused with investigational convalescent plasma as part of the U.S. Food and Drug Administration’s national Expanded Access Program (EAP) for COVID-19.
- The early indicators suggest experimental convalescent plasma is safe in treating severely ill patients.
- At this time, convalescent plasma is the only antibody-based therapy available for COVID-19.
- Patients received plasma between April 3 and May 3. The seven-day incidence of mortality was 14.9%. Sixty-six percent of the patients were in the ICU, and nearly 20% carried the diagnosis of multi-organ dysfunction or failure. Importantly, the reports of serious adverse events related to transfusion of the plasma was small (<1%).
- The researchers note that while the study was not designed to evaluate the efficacy of convalescent plasma, a seven day incidence of mortality of 14.9% in this number of patients indicates “no signal of toxicity beyond what is expected from plasma use in severely ill patients.”
- It is important to note that this is a first safety report and does not provide any findings on the effectiveness of convalescent plasma in the treatment of COVID-19. Also, the EAP is ongoing and data are still being gathered. This is not a clinical trial; there is no control arm.

**Treatment of COVID-19 Patients with Convalescent Plasma** <sup>[41]</sup>,  
Salazar E et al., *The American Journal of Pathology* (2020), doi:  
<https://doi.org/10.1016/j.ajpath.2020.05.014> .

COVID-19 disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally, and no proven treatments are available. Convalescent plasma therapy has been used with varying degrees of success to treat severe microbial infections for more than 100 years. Patients ( $n = 25$ ) with severe and/or life-threatening COVID-19 disease were enrolled at the Houston Methodist hospitals from March 28 – April 14, 2020. Patients were transfused with convalescent plasma obtained from donors with confirmed SARS-CoV-2 infection and had recovered. The primary study outcome was safety, and the secondary outcome was clinical status at day 14 post-transfusion. Clinical improvement was assessed based on a modified World Health Organization 6-point ordinal scale and laboratory parameters. Viral genome sequencing was performed on donor and recipient strains. At day 7 post-transfusion with convalescent plasma, nine patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease.

**Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma, JAMA. 2020 Mar 27, Shen C et al.; Pmid:32219428.** <sup>[3]</sup>

In a limited case series of 5 critically ill patients with laboratory-confirmed COVID-19 and acute respiratory distress syndrome (ARDS) who met the following criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment,  $PAO_2/FIO_2 < 300$  and mechanical ventilation. All 5 were treated with convalescent plasma transfusion. The study was conducted at the infectious disease department, Shenzhen Third People's Hospital in Shenzhen, China, from January 20, 2020, to March 25, 2020; final date of follow-up was March 25, 2020. Clinical outcomes were compared before and after convalescent plasma transfusion.

Patients received transfusion with convalescent plasma with a SARS-CoV-2-specific antibody (IgG) binding titer greater than 1:1000 (end point dilution titer, by enzyme-linked immunosorbent assay [ELISA]) and a neutralization titer greater than 40 (end point dilution titer) that had been obtained from 5 patients who recovered from COVID-19. Convalescent plasma was administered between 10 and 22 days after admission.

All 5 patients (age range, 36-65 years; 2 women) were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5

patients, the SOFA score decreased, and PAO<sub>2</sub>/ FIO<sub>2</sub> increased within 12 days (range, 172-276 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2-specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion.

In this preliminary uncontrolled case series of 5 critically ill patients with COVID-19 and ARDS, administration of convalescent plasma containing neutralizing antibody was followed by improvement in their clinical status. The limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.<sup>[3]</sup>

## 6.2 Use in SARS (Severe Acute Respiratory Syndrome)

### **Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005, 24(1):44-46. Cheng, Y C et al.;<sup>[7]</sup>**

This study involved the treatment of 80 patients with SARS in Hong Kong. Patients treated before day 14 had improved prognosis defined by discharge from hospital before day 22, consistent with the notion that earlier administration is more likely to be effective. In addition, those who were PCR positive and seronegative for coronavirus at the time of therapy had improved prognosis.

SARS was diagnosed according to CDC criteria. Starting in mid-March 2003, patients admitted with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission to cover community-acquired pneumonia. If fever persisted, ribavirin (administered as 1200 mg p.o. t.i.d. or i.v. 400 mg q8h) and prednisolone (0.5–1 mg/kg) were started on day 3. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone (500 mg i.v. daily for 2–3 doses).

Patients whose condition continued to deteriorate, as defined by SaO<sub>2</sub><90% on 0.5 FiO<sub>2</sub>, were then given 200–400 ml (4–5 ml/kg) of ABO-compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. The potential benefits and risks of convalescent plasma were carefully explained to the patients and their families.

Convalescent plasma was obtained from patients who had recovered from SARS patients. Recovery was defined as an afebrile status for at least 7 days, radiographic improvement of 25%, no further need of an oxygen supplement, and at least 14 days following symptom onset. Informed consent was obtained from the donors who needed to be seronegative for hepatitis B and C, HIV and syphilis and seropositive for coronavirus (titer range, 160–2,560).

Good outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death before day 22 or hospitalization beyond 22 days. The discharge criteria of the Hospital Authority were as follows: (i) afebrile status for 4 consecutive days; (ii) improvement in previously abnormal leukocyte counts, platelet counts, creatinine phosphatase kinase, lactate dehydrogenase, liver function tests and C-reactive protein; (iii) radiographic improvement; and (iv) at least 21 days following the onset of illness. This last factor led us to define good outcome as discharge by day 22. Using this definition, we were able to divide the patients into two distinct non-overlapping outcome groups.

The eighty patients (43 females and 37 males) were given convalescent plasma around day 14 (range, 7–30 days) following the onset of symptoms. The median age of the patients receiving convalescent plasma was 45 years (range, 21–82 years). The mean volume of plasma infused was  $279.3 \pm 127.1$  ml (range, 160–640 ml). Thirty-three patients had a good clinical outcome; they were given convalescent plasma earlier than the patients with a poor outcome. Patients given convalescent plasma before day 14 had a better outcome than those given plasma after day 14. The mortality rates in the two groups were 6.3% and 21.9%, respectively. One major factor affecting the timing of convalescent plasma administration was plasma availability. Overall, the mortality rate was 12.5% among the 80 patients given convalescent plasma. The overall SARS-related mortality rate in Hong Kong was 17% (299/1755) during the SARS epidemic from 6 March to 24 May 2003.

Sixty-one percent of the patients with a good outcome were PCR positive and seronegative for coronavirus at the time of plasma infusion as compared with 21% in the group with a poor outcome. The 30 patients who were PCR positive and seronegative for coronavirus at the time of convalescent plasma therapy had a better outcome than those who were already seropositive (66.7% vs 20%). Age was a poor prognostic factor. In the multivariate analysis, only the time of convalescent plasma therapy and coronavirus PCR positivity were significant factors.

No immediate adverse effects were observed with convalescent plasma infusion. There was no correlation between clinical outcome and either the volume of plasma infused or the coronavirus antibody titers of the donors.

### **6.3 Use in H1N1 Influenza**

A cohort study was conducted in Hong Kong by recruiting 93 patients aged >18 years with severe H1N1 2009 infection requiring intensive care.<sup>[8]</sup> All subjects were offered treatment with 500 mL convalescent plasma with a neutralizing H1N1 2009 antibody titer of >1:160, collected from patients recovering from H1N1 2009 infection. Twenty subjects (21.5%) agreed to receive the plasma treatment, and 73 subjects declined. All subjects received standard antiviral treatment and other supportive medical care. Clinical outcome was compared in the subjects treated with plasma with those who declined plasma treatment as the “untreated” controls. Mortality in the treatment group was significantly lower than in the control group (20.0% vs. 54.8%; P = .01). There were no adverse events (AEs) attributed to the convalescent plasma.

A multi-center, prospective, double-blind, randomized controlled trial of a hyperimmune intravenous immunoglobulin was also conducted in Hong Kong.<sup>[9]</sup> Convalescent plasma from patients who recovered from the 2009 pandemic influenza infection was made into an immunoglobulin (H-IVIG). Patients with severe A (H1N1) infection on standard antiviral treatment requiring intensive care and ventilatory support were randomized to receive H-IVIG or normal IVIG. Thirty-five patients were randomized to receive H-IVIG (17 patients) or IVIG (18 patients). H-IVIG treatment was associated with significantly lower day 5 and 7 post-treatment viral load when compared to the control (p=0.04 and p=0.02 respectively). Subgroup multivariate analysis of the 22 patients who received treatment within 5 days of symptom onset demonstrated that H-IVIG treatment was the only factor that independently reduced mortality [OR: 0.14, 95% CI, 0.02-0.92; p=0.04].

### **6.4 Use of Convalescent Plasma Therapy in Other Diseases**

Multiple clinical trials conducted in the Soviet Union reported that convalescent plasma, serum and IVIG were efficacious in the treatment of influenza pneumonia and the prevention of influenza.<sup>[10-15]</sup>

Luke et al. conducted a meta-analysis of studies using convalescent blood products during the Spanish Influenza pandemic of 1918 and concluded that the approach may have been beneficial in the treatment of influenza pneumonia and Acute Respiratory Distress Syndrome (ARDS).<sup>[16]</sup>

A number of other viral diseases are treated with antibody preparations with variable results. These antibody preparations are generally given as IVIG but curative treatment with IVIG is rare. Red blood cell aplasia caused by parvovirus B19 infection is the only recognized viral infection in which treatment with IVIG may eradicate the infection.<sup>[17,18]</sup> However, there is considerable evidence that immune globulin preparations may modify the natural history of viral diseases. These are summarized below.

**Cytomegalovirus (CMV):** CMV enriched immune globulin preparations have shown benefit when used in combination with ganciclovir in the treatment of CMV pneumonia. [19] This immune globulin preparation is also utilized in the treatment of ganciclovir-resistant CMV infections.

**Respiratory Syncytial Virus (RSV):** In adult bone marrow transplant (BMT) patients with RSV pneumonia, combination therapy using aerosolized ribavirin and standard IVIG (500 mg/kg every other day for 12 days) for the treatment had a 22% mortality rate, compared to a historical mortality rate of 70%. [20] In pediatric BMT patients with RSV pneumonia, patients treated with combination aerosolized ribavirin and RSV antibody enriched IVIG (RespiGam®) had a 9.1% mortality, compared with a historical 50-70% mortality rate of such patients given ribavirin alone. [21]

**Vaccinia Virus:** Certain complications of vaccination with the vaccinia virus (smallpox vaccine) are treated with vaccinia immune globulin (VIG). These included generalized vaccinia, eczema vaccinatum, and progressive vaccinia. There have been no controlled trials of the efficacy of VIG. However, anecdotal experience suggests that treatment with VIG for these conditions is beneficial, and is now considered the standard of care. [22]

**Hepatitis A:** IVIG has also been shown useful in hepatitis A. Persons who have been recently exposed to hepatitis A and who have not been previously vaccinated with hepatitis A are recommended to receive standard IVIG as post-exposure prophylaxis. This is based on data that showed IVIG, when administered within 2 weeks following an exposure to hepatitis A, is greater than 85% effective in preventing hepatitis A. [23] IVIG can also attenuate the clinical expression of hepatitis A infection when given later in the incubation period. [24] Standard IVIG is used because it does contain sufficient anti-hepatitis A antibodies.

**Hepatitis B:** For patients with hepatitis B and cirrhosis undergoing orthotopic liver transplant, hepatitis B hyperimmune IgG is given pre-operatively and post-operatively to prevent reinfection with hepatitis B. This has been shown to be 50-85% effective in preventing recurrence of hepatitis B in the transplanted liver. [25,26] This efficacy may be improved with the concurrent use of the antiviral lamivudine. [26]

**Rabies:** Rabies hyperimmune IgG is the standard recommended therapy after exposure to the rabies virus/rabid animal. [27]

**Argentine Hemorrhagic Fever:** Convalescent plasma from survivors is the standard of care and has been shown to reduce mortality from 50% to 4% if therapy is initiated within eight days of disease onset. [28]



## **7 Biohazard Information**

This material should be handled as if capable of transmitting infectious agents. Please use universal precautions. No test method can provide total assurance that Hepatitis B Virus, Hepatitis C Virus, Human Immunodeficiency Virus, or Other Infectious Agents are absent. Thus, all biological products that we provide should be handled at the Bio-Safety Level 2 as recommended by the CDC/NHI Manual “Biosafety In Microbiological And Biomedical Laboratories, From Potentially Infectious Human Serum Or Blood Specimens”.

## **8 Risk / Benefit Analysis**

### **8.1 Benefits**

The benefits of COVID-19 Convalescent Plasma therapy in patients actively infected with SARS-Co V-2 are unknown. However, it is possible that CCP in addition to other standard of care treatments or investigational antiviral therapy will more rapidly decrease viral replication, reduce the duration and severity of illness, reduce complications, and improve outcomes after infection with SARS-Co V-2.

### **8.2 Risks**

#### **8.2.1 Side Effects and Hazards for Plasma**

Side effects from plasma and plasma components are listed in the Circular of Information for Human Blood and Blood Components (2017) <sup>[29]</sup>

Hazards that pertain to transfusion of FFP can be classified as:

- Immunologic Complications, Immediate
  - Hemolytic transfusion reaction
  - Febrile nonhemolytic reaction
  - Allergic reactions
  - Anaphylactoid/anaphylactic reactions
  - Transfusion-related acute lung injury (TRALI)
- Immunologic Complications, Delayed
  - Posttransfusion purpura
- Nonimmunologic Complications
  - Transmission of infectious diseases
  - Bacterial sepsis
  - Transfusion-associated circulatory overload (TACO)
  - Hypothermia
  - Metabolic complications

ABO compatible convalescent plasma will be transfused preferentially. If ABO compatible convalescent plasma is not available, investigators may follow their institution's guidelines for administration of incompatible plasma with respect to ABO mismatch, titer, and volume limits.

Do not use FFP if there is evidence of container breakage or of thawing during storage. FFP must be thawed in a waterbath at 30-37C or in an FDA-cleared device. If a waterbath is used, thaw the component in a protective plastic overwrap using gentle agitation.

Common risks of plasma transfusions may include one or more of the following: fever, rash, hives, or headache. Other more serious risks are rare and may include the following: serious allergic reactions including anaphylaxis, bacterial infections, or viral infections like Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV).

Transfusion-related acute lung injury (TRALI) may occur, but this risk will be minimized by using male donated plasma or female donors who have not been pregnant or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.. TRALI is characterized by a clinical constellation of symptoms including dyspnea, hypotension and fever. Although the precise pathogenesis of TRALI remains unknown, it has been shown to be most often related to the transfusion of anti-HLA and anti-neutrophil antibodies from plasma from multiparous women (antibodies presumably generated during pregnancy) or donors who have received multiple blood transfusions. The risk of TRALI is reported as 1 out of 5000 transfusions.<sup>[30]</sup>

Each unit of plasma contains 200-400 mL of volume. Depending on the total volume infused, there is the risk of volume overload in the recipient that could cause pulmonary edema. Transfusion-associated circulatory overload (TACO) has been associated with plasma infusion and may be clinically indistinguishable from TRALI even though the physiologic mechanisms differ.<sup>[31]</sup> TACO is hydrostatic not permeability edema and more responsive to diuresis when it occurs. Subjects with preexisting conditions who may not tolerate this volume of plasma will be excluded from this study, but this condition could still occur in recipients.

There are case reports of pulmonary emboli occurring after administration of IVIG and plasma therapy, though definitive studies assessing risk are lacking.<sup>[32]</sup> Pulmonary emboli have been shown to develop in approximately 10-15% of critically ill adults.<sup>[33]</sup> However, the potential risk of pulmonary embolism exists.

There is the risk of other infections that can be transmitted by blood products. In all cases, the study plasma will follow FDA guidance for donor screening and testing of plasma products. Zika virus is one such possible infection. As of November 2017, there has been no documented transmission associated Zika virus infection in the United States. Universal testing for Zika virus was implemented at the end of November 2016. The risk of transfusion associated Zika virus infection is considered low.

There is a theoretical risk of antibody-dependent enhancement of disease and suppressed long-term immune response.<sup>[34-36]</sup>

## **8.2.2 Side Effects and Risks Associated with COVID-19 Disease**

There is initial emerging evidence in disease progression of patients with COVID-19 disease that there is a potential for increased risk of cardiac arrhythmias.

Various cardiac arrhythmias associated with COVID-19 infection and treatment that may not correlate with severity of lung injury on CXR. In patients presenting with symptoms of COVID-19 infection, clinicians need to be wary of the potential for significant, often life-threatening arrhythmias, particularly if fulminant myocarditis is also suspected, and perform appropriate rhythm monitoring. Likewise, when making decisions regarding choice of antiarrhythmics, ionotropes and vasopressors, clinicians need to keep in mind potential proarrhythmic effects of antimalarial and antibiotic therapies currently being investigated as therapeutic agents against COVID-19 disease. <sup>[37-38]</sup>

Along with the previously mentioned risk of plasma therapy associated with pulmonary embolism, there is potential for increase of overall thrombotic or thromboembolic events.

COVID-19 disease causes not only hypercoagulability but also fibrinolysis shutdown which is associated with VTE, stroke, and renal failure. <sup>[39]</sup>

## **9 Summary of Data and Guidance for the Treating Physicians**

There is no known benefit to administering the COVID-19 Convalescent Plasma to infected patients. The plasma will be stored, prepared and administered by standard hospital practices associated with the administration of plasma.

Until there is an approved indication for COVID-19 Convalescent Plasma as a treatment, this product must only be administered to patients properly consented and registered in this Expanded Access Program being executed in accordance with applicable Federal regulations and in accordance with the inclusion and exclusion criteria specified in the study protocol.

Along with the Circular of Information for the Use of Blood and Blood Components (2017)<sup>[29]</sup>, the NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol v2.5.2<sup>[40]</sup> can be used to assess transfusion-associated adverse reactions. This document can assist in classification of the reaction-specific case definition, severity, and imputability criteria.

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