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TITLE: Safety and Pharmacokinetics of Anti-SARS-CoV-2 Human Convalescent Plasma in High-risk Children

Institution: Johns Hopkins University

Resources: Convalescent Plasma – Adult Study

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1. OBJECTIVE

The purpose of this study is to evaluate the safety and pharmacokinetics of high-titer anti-SARS-CoV-2 human plasma (i.e., convalescent plasma) in children (age 1 month to 18 years) who are at high-risk for disease progression.

1.1 Primary Objective:

Evaluate the safety of treatment with high-titer anti-SARS-CoV-2 human plasma (i.e., convalescent plasma) in children (age 1 month to 18 years) exposed or infected with SARS-CoV-2.

1.2 Primary Safety Endpoints:

- Cumulative incidence of grade 3 and 4 adverse events (AE) during the study period.
- Cumulative incidence of serious adverse events (SAE) during the study period.

1.3 Secondary Objectives:

- Evaluate the response of high-titer anti-SARS-CoV-2 human plasma in children (1 month old to 18 years old) exposed or infected with SARS-CoV-2.
 - a. Confirmed SARS-CoV-2 infection: (i) Evaluate outcome of disease severity during the study period (descriptive analysis of several measurable outcomes, e.g. disease worsening, hospitalization, need for supplemental oxygenation, respiratory distress, requirement for mechanical ventilation, and death). (ii) RT-PCR (Ct) values before and after plasma treatment.
 - b. High-risk exposure: Cumulative incidence of asymptomatic, mild, moderate and severe COVID-19 disease confirmed by nasopharyngeal PCR.
- Characterize preliminary pharmacokinetics on the persistence of anti-SARS-CoV-2 antibodies after administration of high-titer anti-SARS-CoV-2 human plasma: anti-SARS-CoV-2 antibody titers at 7, 14, and 21-28 days post-treatment stratified by age groups.
- Evaluate for possible modification high-titer anti-SARS-CoV-2 human plasma might have on the natural antibody response to SARS-CoV-2 infection: anti-SARS-CoV-2 antibody titers at 60-120 days post-treatment stratified by age groups.

2. BACKGROUND AND RATIONALE

2.1 Experience with the use of convalescent plasma

There are currently no proven treatment or prophylaxis options for COVID-19, which is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Human convalescent plasma has been successfully used for infection prevention and treatment of many infections^{1,2}. Maternal antibodies render protection in infants for various infections^{3,4}. Furthermore, immunoglobulins are also routinely used in clinical practice to prevent infections (e.g., rabies, hepatitis B, chickenpox, etc.) in exposed, susceptible children⁵. Previous studies have demonstrated that human convalescent plasma has neutralizing antibodies to viruses⁶. Treatment with convalescent plasma reduced mortality in patients with the Spanish flu⁷, the severe pandemic influenza A (H1N1) 2009 virus infection^{8,9}, the Ebola virus outbreak¹⁰, SARS-CoV-1 in 2003^{11,12}, and MERS in 2013¹³. Thus, human convalescent plasma may provide an option for the prevention and treatment of COVID-19, and could be rapidly available from people who have recovered from the disease and can donate plasma. Two recent reports from China on 15 adults (age range 34-78) demonstrated that human convalescent plasma derived from COVID-19 recovered subjects was safe and without any AEs^{14,15}.

Recently (March 24, 2020), the U.S. FDA approved a program for use of investigational COVID-19 convalescent plasma under emergency IND for those with severe or immediately life-threatening COVID-19¹⁶. Unfortunately, human convalescent plasma may not be as beneficial for severely affected individuals, as early treatment or prophylaxis have been found to be more effective using this approach^{7,17}. A protocol for the use of COVID-19 convalescent plasma in adults to prevent infection in asymptomatic individuals has

received U.S. FDA approval on April 6th. Other protocols, for the early treatment of symptomatic adults are under consideration. All of these exclude children. Therefore, there are no active protocols for the use of convalescent plasma in children presenting in the early stages of disease or for prophylaxis.

2.2 Rationale for Pediatric Studies

While children usually develop milder COVID-19 disease, some groups of children with COVID-19 may have a higher risk of disease progression due to underlying conditions - immunosuppression, lung disease and cardiovascular disease. A recent report from the U.S. Centers for Disease Control and Prevention (CDC) demonstrates that while many cases in children are mild, serious illness resulting in hospitalization and death still occur¹⁸. During the period between February 12th and April 2nd, 2,572 pediatric cases (children <18 years) have been reported in the US. Information on hospitalization status was available for 745 (29%) cases in children aged <18 years and 35,061 (31%) cases in adults aged 18–64 years. Among children with COVID-19, 147 (estimated range = 5.7%–20%) were reported to be hospitalized, with 15 (0.58%–2.0%) admitted to an intensive care unit (ICU). Children aged <1 year (infants) accounted for the highest percentage (15%–62%) of hospitalization among pediatric patients with COVID-19. Among 95 children aged <1 year with known hospitalization status, 59 (62%) were hospitalized, including five who were admitted to an ICU¹⁸. This is similar to a report from China suggesting that infants may have a worse course¹⁹. Among 345 pediatric cases with information on underlying conditions, 80 (23%) had at least one underlying condition. The most common underlying conditions were chronic lung disease (including asthma) (40), cardiovascular disease (25), and immunosuppression (10)¹⁸. Among the 295 pediatric cases for which information on both hospitalization status and underlying medical conditions was available, 28 of 37 (77%) hospitalized patients, including all six patients admitted to an ICU, had one or more underlying medical condition; among 258 patients who were not hospitalized, 30 (12%) patients had underlying conditions. Three deaths have been reported during this time period, although review of these cases is ongoing to confirm COVID-19 as the likely cause of death. CDC reported that as of April 2, 2020, the number of COVID-19 cases in children continues to increase¹⁸. Another report based on real-time data from over 140 hospitals, showed there were 74 children admitted to ICUs by April 6th²⁰. *These data underscore the need for COVID-19 disease prevention and treatment strategies for certain Pediatric sub-populations with underlying conditions (defined as high-risk children in this study – section 3.1 below).*

Childhood outbreaks may also drive larger, population-wide outbreaks. *Young children, including asymptomatic children¹⁸, especially those in daycare or preschool, are likely to infect other children. This would not only be a risk to children with certain underlying conditions (see definition of high-risk children in section 3.1), but also to close- or household-contacts (e.g. ≥65-year-old grandparents, caregivers) of these children.* Therefore, until proven therapeutics or vaccines are available, prophylaxis (and social distancing) may remain as the only method to control these outbreaks and prevent infections of high-risk individuals.

While human convalescent plasma is likely to be effective in children, information regarding the safety of such treatment in children is needed. Data from many diseases also indicates that the pharmacokinetics of exogenously administered drugs, biologics, and blood products is different in children. The purpose of this study is to evaluate the safety and pharmacokinetics of human convalescent plasma in high-risk children (age 1 month to 18 years). The proposed study will also provide important data for immunoglobulin-based treatments (that are likely to be developed in the near future) to prevent or treat COVID-19.

3. SUBJECT SELECTION:

3.1 Eligibility Criteria

Inclusion criteria: Subjects may be enrolled only if all of the following criteria are met:

1. Between 1 month and 18 years of age at the time of consent.

2. Determined to be at high-risk for severe SARS-CoV-2 disease based on the American Academy of Pediatrics definition of immunocompromised children⁵ and reported high-risk Pediatric sub-populations^{18,19,21}. These include any of the following:
 - a. Immunocompromised: primary or acquired immunodeficiency e.g. recipient of a bone marrow or solid organ transplant in the last 12 months (or at any time if concurrent with graft-versus host disease), recipient of chemotherapy for a malignancy within the past 6 months, HIV with CD4 (<30% for ≤12 months old; <25% for 12–35 months; <20% for 36–59 months or <350 for all other ages), receiving immunosuppressive or immunomodulatory treatments (e.g., high-dose steroids [≥2 mg/kg/day of systemic prednisone or equivalent for ≥14 days], tacrolimus, sirolimus, cyclosporine, antithymocyte globulin - ATG, mycophenolate, methotrexate, etc.)
 - b. Hemodynamically significant cardiac disease (e.g. congenital heart disease)
 - c. Lung disease with chronic respiratory failure (e.g. patients with asthma, cystic fibrosis, bronchiectasis, chronic lung disease of prematurity, tracheostomy / ventilator dependency, restrictive lung disease, severe neuromuscular disease, etc.)
 - d. Medically complex children - defined as children who have a long-term dependence on technological support (including tracheotomy) associated with developmental delay and/or genetic anomalies²¹
 - e. Obesity - defined as children with a body mass index (BMI) at or above the 95th percentile for children and teens of the same age and sex^{22,23}
 - f. Infant, i.e. child ≤1 year old^{18,19}
3. Confirmed SARS-CoV-2 infection OR high-risk exposure as defined:
 - a. Confirmed infection: Child who tested positive for COVID-19 and is no more than 168 hours after onset of symptoms (and within 192 hours at the time of receipt of plasma).
 - b. High-risk exposure: Susceptible child who was not previously infected or otherwise immune to SARS-CoV-2 and exposed within 96 hours prior to enrollment (and within 120 hours at the time of receipt of plasma). Both criteria below should be met:
 - A household member or daycare center (same room) exposure to a person with [confirmed SARS-CoV-2 OR with clinically compatible disease in regions with widespread ongoing transmission]
 - Negative for SARS-CoV-2 (nasopharyngeal swab)
4. Subject is judged by the investigator to have the initiative and means to be compliant with the protocol.
5. Subjects or their legal guardians must have the ability to read, understand, and provide written informed consent for the initiation of any study related procedures.

Exclusion criteria: Subjects will be excluded from enrollment if any of the following apply:

1. History of severe reactions (e.g. anaphylaxis) to transfusion of blood products. Subjects with minor reactions such as fever, itching, chills, etc. that resolve spontaneously or respond to pre-medications, and that do not represent more significant allergic reactions will not be excluded.
2. Female subjects in child-bearing age with a positive pregnancy test, breastfeeding, or planning to become pregnant/breastfeed during the study period.
3. Subject / legal guardian deemed by the study team to be non-compliant with the study protocol.

3.2 Inclusion of Women and Minorities: Male and female children of all races and ethnic groups are eligible for this trial and encouraged to participate.

4. CANCELLATION/WITHDRAWAL PROCEDURES

4.1 Cancellation Guidelines: If a subject does not receive an injection of the convalescent plasma, the subject may be canceled. Reasons for cancellation must be submitted in writing to the Principal Investigator. Note: A subject may only be canceled if no convalescent plasma is administered.

4.2 Withdrawal of Consent: Subjects may voluntarily withdraw consent at any time or for any reason during the study without effect on their further management / treatment. However, if a subject withdraws consent within the first weeks after receiving the convalescent plasma, they should continue to be evaluated for AEs.

4.3 Withdrawal of a Subject by the Investigator: Subjects may be withdrawn from the study, prior to any dose of convalescent plasma, by the investigator if deemed medically necessary. The investigator may withdraw subjects if they are lost to follow up, non-compliant with study procedures or if the investigator determines that continued participation in the study would be harmful to the subject or the integrity of the study data. The reason for withdrawal from the study should be adequately documented.

5. INVESTIGATIONAL PLAN

5.1 Recruitment: Stratification by age groups (1 month to 5 years; 5-12 years; 12-18 years) would be performed to attain similarly sized groups. Up to 30 subjects will be prospectively enrolled and will receive anti-SARS-CoV-2 human plasma (~10 per age group category). Subjects will be screened for symptoms at post-enrollment. SARS-CoV-2 nasopharyngeal swab and blood for titers will be obtained prior to convalescent plasma administration and at 7, 14, 21-28 and 60-120 days thereafter. The study investigators or other study personnel (including study coordinators) will determine eligibility and discuss the study with eligible subjects. Combined informed consent and HIPAA privacy authorization will be obtained if subjects wish to participate in this study.

5.1.1 Study Calendar

Procedures	Screening/ Baseline ¹	Transfusion ²	Follow up			
			7	14	21-28	60-120 ³
Day	-7 to 0	0	7	14	21-28	60-120 ³
Eligibility						
Informed consent	X					
COVID-19 symptom screen	X	X	X	X	X	X
Determination of eligibility as per inclusion/exclusion criteria	X					
Demographic and medical history	X					
Serum pregnancy test if female of child-bearing age (i.e. post-menarche)	X					
Blood typing	X					
Study Procedures						
Concomitant medications	X	X	X	X	X	
Vital signs		X ⁴				
Physical evaluation		X ⁸				
Height, weight		X				
Follow up phone call			X	X	X	X
Adverse events monitoring		X	X	X	X	
Laboratory testing						
CBC ⁵	X					
Comprehensive metabolic	X					

panel ⁵						
SARS-CoV-2 RT-PCR of nasopharyngeal aspirate or swab ^{5,6}	X	X	X	X	X	
Serological testing (anti-SARS-CoV-2 titers) ^{5,6,7}		X	X	X	X	X
Study Plasma Administration						
Study plasma infusion		X				

¹ Assessments that have been performed as part of standard care, prior to obtaining informed consent AND that are within 7 days of administration of the study drug, may be used for screening.

² Participant with confirmed SARS-CoV-2 infection (by NP swab RT-PCR) will receive plasma transfusion within 192 hours. Exposed participants, will receive plasma transfusion provided they have been exposed within the past 120 hours prior to transfusion and tested negative for SARS-CoV-2. Optional: If plasma transfusion is not available within the specified timeframe for participant, participant who is not able to receive plasma will be asked to continue study participation. Continuation of study participation will consist of follow-up COVID-19 symptom screening, clinical assessment, and serological testing (anti-SARS-CoV-2 titers) on Day 0, Day 7, Day 14, between Day 21-28 and between Day 60-120, and collection of nasopharyngeal swabs for SARS-CoV-2 RT-PCR on Day 0, Day 7, Day 14, and between Day 21-28. These analyses are exploratory to study the rate of SARS-CoV-2 positivity and antibody response to SARS-CoV-2 infection. The analysis is primarily descriptive. These participants will not be counted towards our sample size of 30, since they will have not received any study plasma.

³ Day 60-120 blood sample will be exploratory and used to test whether there is endogenous (host) antibody production against SARS-CoV-2. The assumption is that by days 60-120, the levels of exogenously administered antibodies (via convalescent plasma) would have decayed, and high titers at this time point would be suggestive of endogenous antibody production.

⁴ Vital sign testing: Immediately prior to infusion, 10-20 minutes after the start of the infusion, at the completion of infusion and 30-60 minutes after the end of the infusion.

⁵ Safety laboratory tests taken (CBC, CMP) and NP swabs collected for baseline will be performed at the local JHH CLIA-certified clinical laboratory.

⁶ Serological testing (anti-SARS-CoV-2 titers) will be collected for research purposes. Research bloods will be processed at the Jain research lab. Research NP swab for SARS-CoV-2 RT-PCR on Day 0 will only be collected for participants with confirmed SARS-CoV-2 infection (by NP swab RT-PCR). Research NP swabs for SARS-CoV-2 RT-PCR will be processed in the Pekosz research lab.

⁷ On day of transfusion (day 0) two blood samples will be taken for serology, one prior to plasma administration and an additional blood sample will be obtained 30 min following administration of plasma. This sample would be 1-6 ml in volume, provided the maximum allowable blood draw for participants based on each participant’s weight (kg) is maintained. **Blood draw will be limited to 2 ml/kg in any 24 hr. period**

⁸ If a physical exam is assessed as part of standard care within 7 days before transfusion and results are deemed consistent with patient’s current status on Day 0 by study team member, it is not to be repeated.

5.2 Pre-Study and Post-Study Evaluations:

Medical history and physical examination with vital signs and laboratory tests. The prestudy evaluation will be performed within 7 days prior to the administration of the study plasma. Post-study evaluation will be completed after administration of study plasma as shown in the study calendar.

5.2.1 Pre-study Evaluations

- a. COVID-19 symptom screen: children and their caregivers will be asked if the subject had fever, cough, shortness of breath, sore throat, rhinorrhea, vomiting, headache, rash, nasal congestion, diarrhea, muscle aches, loss of taste or smell, need for supplemental oxygenation, or required mechanical ventilation in the past 7 days.

- b. Medical history: timing of exposure to COVID-19 source patient, acute and chronic medical condition, allergies.
- c. Concomitant medications will be documented, including prescription medications, over the counter medications, herbal treatments, nutritional supplements, and blood products.
- d. Review prior history of blood product administration in the past and any history of reaction to blood transfusion.
- e. Blood typing (assessment of ABO type on file), CBC with differential and a comprehensive metabolic panel (including BUN, creatinine, alkaline phosphatase, total bilirubin, AST and ALT). To reduce the need for additional blood sampling, blood tests available for up to 7 days before the administration of study plasma can be considered for this study.
- f. If the subject is a female of child-bearing potential (i.e. post- menarche), qualitative hCG serum pregnancy test will be performed. Initiation of menstruation will be established by asking date of any and last menstrual period.
- g. COVID-19 testing (SARS-CoV-2 RT-PCR) prior to infusion, from nasopharyngeal, throat and / or stool (optional) samples. If the results are not already available due to clinical care of the subject, the study team will arrange for this testing to be performed. Patients with positive or negative results will still get the study plasma but will be assigned to an analysis group (contact exposure or confirmed infection) once the results are available.
- h. Serological testing for anti-SARS-CoV-2 antibody titers prior to infusion
- i. Screening procedures will be completed at the Johns Hopkins Facility Community Collection Sites and Field Units. The Bayview COVID Overflow clinic and the Johns Hopkins Children's Center's ambulatory clinics or facilities will also be utilized when necessary. Screening procedure location for each subject will depend on his or her needs, location, and COVID-19 status and in accordance with the JHH HEIC guidelines.
- j. All NP swabs will be collected at a Johns Hopkins Medicine Health Care Epidemiology and Infection Control (HEIC) approved site. Patient interactions with study staff, testing and specimen collection will be conducted in accordance with the Johns Hopkins HEIC policies for managing patients with recent COVID exposure, and protection for study staff (mask, PPE when required) as appropriate. The HEIC protocols are:
https://intranet.insidehopkinsmedicine.org/heic/novel_coronavirus/clinical_resources
https://intranet.insidehopkinsmedicine.org/heic/docs/2019-nCoV_outpatient_guidelines.pdf
https://intranet.insidehopkinsmedicine.org/heic/docs/2019-nCoV_patient_discharge_protocol.pdf

5.2.2 Study Drug Administration and Post-study Evaluations

- a. Plasma transfusions for Johns Hopkins site participants: For hospitalized inpatients, transfusions will be performed at their respective units within the Johns Hopkin's Children Center. For non-hospitalized patients, transfusion location depend on the subject's patient COVID risk cohort. Transfusions for SARS-CoV-2 RT-PCR negative subjects who are asymptomatic will take place at The Adult Clinical Research Unit (CRU) on Blalock 3 at Johns Hopkins Hospital. Transfusions for SARS-CoV-2 RT-PCR positive subjects or for subjects who are considered to be patients under investigation (PUI) will take at the Johns Hopkins Hospital Pediatric Emergency Department or any of the biomode units set up by Johns Hopkins that has the capacity and ability to administer transfusions to subjects per JH policy. This includes, but not limited to, the biomode units at JH Pediatric Infusion Clinic, SKCCC, Greenspring, and BMC. Each transfusion location for PUIs and SARS-CoV-2 RT-PCR positive patients will be in accordance with the JHH HEIC guidelines.
- b. Participants' follow-up procedures will be completed at the Johns Hopkins Facility Community Collection Sites and Field Units. The Bayview COVID Overflow clinic and the Johns Hopkins

Children's Center's ambulatory clinics or facilities will also be utilized when necessary. Follow-up procedure location for each subject will depend on his or her needs, location, and COVID-19 status and in accordance with the JHH HEIC guidelines. The HEIC guidelines on this subject are available here: https://intranet.insidehopkinsmedicine.org/heic/docs/2019-nCoV_ambulatory_confirmed_returning_to_facility.pdf

- c. Nurse practitioners or registered nurses (RN's) will administer the infusion per JH policy. They will attend to the participant throughout the infusion and post infusion observation period. A study physician or advanced practice clinician with clinical privileges at JH will be available by phone and within 5 minutes physical response time to respond to any emerging event during the infusion.
- d. Subjects will be assessed for AEs after the administration of the study plasma and at the day of infusion and on days 7, 14, 21 and 28, after infusion.
- e. COVID-19 symptom screen: children and their caregivers will be asked if the subject had fever, cough, shortness of breath, sore throat, rhinorrhea, vomiting, headache, rash, nasal congestion, diarrhea muscle aches or loss of taste or smell.
- f. Assessment of clinical status (composite outcome of disease severity: disease worsening, hospitalization, need for supplemental oxygenation, respiratory distress, requirement for mechanical ventilation, and death).
- g. COVID-19 testing (SARS-CoV-2 RT-PCR) and blood draw for anti-SARS-CoV-2 antibody titers at day 7, 14, 21-28 and 60-120.

5.3 Blood product and rationale for doses

5.3.1 Collection

All activities pertaining to donor recruitment, enrollment, and collection and processing will take place at an FDA licensed blood collection site. [e.g. New York Blood Center (NYBC) or similar FDA licensed blood collection site]. These facilities will be U.S. Food and Drug Administration (FDA)-licensed and AABB (American Association of Blood Banks) accredited attesting to robust quality oversight of all operations. COVID-19 convalescent plasma will only be collected from recovered individuals if they are eligible to donate blood (21 CFR 630.10, 21 CFR 630.15).

5.3.2 Plasma processing

- Standard apheresis plasma collection will be performed per routine standard operating procedure at the collection facility
- As per routine practice, samples will be collected at time of donation for testing for transfusion-transmissible infections (all donors), ABO and red cell antibodies (all donors) and HLA antibodies (female donors).
- Target collection volume: ~450-600mL; this will allow for later splitting (separation) into 200-250mL daughter units
- The plasma will be processed per routine practice; it will be frozen within 24hrs of collection per AABB standards
- The plasma will be maintained in quarantine at the blood center pending laboratory test results (i.e. infectious screening, ABO and RhD status, Red cell and HLA antibodies)
- If laboratory testing is acceptable (i.e. negative infectious and antibody screening), the products will be distributed to hospital blood bank for storage
- In the event of an abnormal test result, the product will be discarded and the donor will be notified by the blood center as is standard practice.
- The study product provided for this study are for use only as directed in the study protocol.

5.3.3 Rationale for dosing

The current FDA recommendations target titers that are optimally greater than 1: 320 if testing is available. Dose calculation are based on 1 unit (200-250 mL) of plasma with anti-SARS-CoV-19 titers of $\geq 1:320$. Previous experiences treating SARS-CoV-1 with convalescent plasma, where 5 mL/kg of plasma with anti-SARS titer $\geq 1:160$ was utilized¹¹. However, we have favored a more conservative $\geq 1:320$ given findings from a pilot study in China that showed most (39/40) convalescent donors had titers $\geq 1:160$ ²⁴.

Assuming that SARS-CoV-2 neutralizing antibody titers would be $\geq 1:320$ and based on a first-order linear proportionality, dosing will be calculated for each patient based on the following equation: $10 \text{ mL/kg} * (160/320) = 5 \text{ mL/kg}$. For example, the dose to be administered to a 10 kg subject for treatment would be 50 mL. [$10 \times (160/320) = 5 \text{ mL/kg} \times 10 \text{ kg} = 50 \text{ mL}$].

As the volume of plasma needed per child may be much lower than a unit, if feasible, the same unit would be used amongst more than one subject. *However, plasma from only a single donor will be utilized for each subject.* We will utilize 1-2 unit (200-250 mL per unit) of plasma, but the total volume (mL) infused will be based on weight (kg) with a maximum volume of 500 mL.

5.4 Study Procedures

1. A study investigator or study coordinator will review the study, including the eligibility criteria with the potential subject, and schedule the subject for an informed consent and screening visit if they are deemed an acceptable candidate.
2. Informed consent will be obtained, and pre-study screening evaluations will be obtained. Informed consent from legal guardians of pediatric patients will be taken as set forth in FDA 45CFR 46.405 (21CFR50.52),
3. Eligibility verification: subjects must meet all of the eligibility requirements listed in Section 3.1 before proceeding with the study.
4. A peripheral intravenous catheter will be placed (or an existing central line) to infuse the study plasma.
5. A blood sample will be obtained. The volume (mL) of blood obtained will be based on the minimum sample required for screening laboratory tests. This would be proceed as indicated below for blood typing (ABO), if not already known, complete blood count (CBC) and complete metabolic panel (CMP) as indicated below. A minimum of 0.5 ml will be needed per sample for anti-SARS-CoV-2 titers. The remaining volume will be aliquoted in 500uL vials and frozen for future studies.
6. Vital signs (blood pressure, heart rate, respiratory rate) will be taken prior to administration of the study plasma.
7. Continuous pulse oximetry subject monitoring will be performed during the administration of the study plasma.
8. Study plasma administration will be conducted at the Johns Hopkins Children Center for admitted eligible children. For prophylaxis or treatment of otherwise not admitted children, plasma would be administered at a Johns Hopkins out-patient facilities dedicated to treatment with convalescent plasma, in accordance to the Johns Hopkins adult study. This would be supervised by the pediatric transfusion center with excellent expertise and abundant experience in the administration of blood products to pediatric patients. Transfusions will be performed by qualified/skilled personnel to transfuse children and in settings equipped to handle potential complications of the transfusion.
9. Patients who tested positive for COVID-19 or patients with symptoms concerning for COVID-19 (fever or cough or shortness of breath) will be seen in a facility equipped to see positive patients by staff trained in the appropriate personal protective equipment (PPE). In particular, staff interacting with patients suspected or known to have COVID-19 will be trained and observe airborne precautions with gown, gloves and eye protection. Once patients meet criteria to be seen in ambulatory settings with COVID-19 precautions, then these patients will be seen in the routine

research clinic or primary clinic facility as per Hospital Epidemiology Infection Control defined return to ambulatory care criteria.

10. Pretreatment to minimize transfusion reactions (e.g. acetaminophen, diphenhydramine) may be given as needed or if the patient had previously received pre-medication for blood product administration.
11. The volume (mL) of plasma will be transfused using weight- (kg) based dosing (outlined above) and will be infused at a starting rate of 5mL/kg/hour for 15 minutes. If tolerated well, the remainder of the dose will be infused at a rate of 10 mL/kg/hours. Time at start and end of infusion will be recorded, and vital signs will be measured immediately prior to infusion, 10-20 minutes after the start of the infusion, at the completion of infusion, and 30-60 minutes after the end of the infusion.
12. If an AE develops during infusion, the infusion may be slowed or stopped as per the investigator's discretion.
 - a. Classification of transfusion-associated AE will follow the CDC National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol (<https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf>)
 - b. Management of transfusion-associated AE will follow AABB guidelines; Outside of a simple allergic transfusion reaction, the transfusion will be discontinued and investigated appropriately (i.e. per standard practice guidelines).
13. Post-study evaluation will be completed after the administration of the study plasma.

5.5 Study Statistics

- 5.5.1 **Primary Endpoint:** Evaluate the safety of treatment with high-titer anti-SARS-CoV-2 plasma in children (1 month to 18 years) exposed or infected with SARS-CoV-2.
- 5.5.2 **Sample size:** We plan to enroll a total of up to 30 subjects who will receive anti-SARS-CoV-2 human plasma (~10 per age group category).
- 5.5.3 **Early Stopping Guideline for Safety:** The safety and tolerability will be assessed on an ongoing basis during the course of the study. Follow-ups will include a history and laboratory studies. Study Member will follow-up by telephone (or chart review) to inquire about any AEs. Subsequent subjects will be enrolled as long as there is no reported serious unexpected serious adverse event associated with study plasma. Any serious AE that is definitely or probably related to the plasma administration would cause the study to be suspended and reviewed for continuation.
- 5.5.4 **Analysis of adverse events (AE):** Analysis of AE data will primarily be descriptive based on MedDRA coding of events. The proportion of subjects experiencing an SAE event and the proportion experiencing a Grade 3 or higher will be analyzed.
- 5.5.5 **Analysis of anti-SARS-CoV-2 titers:** Analysis of titers will also be primarily descriptive, comparing the geometric mean titers at the various time points.
- 5.5.6 **Analysis of rates and duration of SARS-CoV-2 PCR Positivity**
Analysis of rates and duration of SARS-CoV-2 PCR positivity will be primarily descriptive as well.

5.6 Endpoints

- 5.6.1 **Primary endpoint:**
Safety of treatment with high-titer anti-SARS-CoV-2 plasma in children (1 month to 18 years) exposed or infected with SARS-CoV-2 (evaluated up to day 28 post-administration of study plasma).
 - a. Cumulative incidence of grade 3 and 4 AEs during the study period
 - b. Cumulative incidence of SAEs during the study period
- 5.6.2 **Secondary endpoints:**
 - a. Efficacy endpoint:

- Confirmed SARS-CoV-2 infection: (i) Evaluate outcome of disease severity during the study period (descriptive analysis of several measurable outcomes, e.g. disease worsening, hospitalization, need for supplemental oxygenation, respiratory distress, requirement for mechanical ventilation, and death). (ii) RT-PCR (Ct) values before and after the study plasma treatment.
 - High-risk exposure: Cumulative incidence of asymptomatic, mild, moderate and severe COVID-19 disease confirmed by nasopharyngeal PCR.
- b. Virologic measures:
- Rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) at days 0, 7, 14 and 21-28.
 - Peak quantity levels of SARS-CoV-2 RNA (Ct values) at days 0, 7, 14 and 21-28.
- c. Pharmacokinetic measures: anti-SARS-CoV-2 antibody titers at days 0, 7, 14, and 21-28, stratified by age groups (1 month to 5 years; 5-12 years; 12-18 years). Anti-SARS-CoV-2 antibody titer measurements will be evaluated by descriptive statistics and non-compartmental or compartmental pharmacokinetic methods will be applied (Phoenix Win Nonlin software; Pharsight A Cetara Company, Cary, NC)²⁵. Individual maximum serum concentration (Cpmax) and time to reach Cpmax (Tmax) values will be obtain by visual inspection of the semi-logarithmic plots of titer concentration versus time. Area under the concentration versus time (AUC) will be calculated by the log-linear trapezoid method. The elimination rate constant will be determined from the slope of the terminal phase of the titer concentration vs time curve using uniform weight. The elimination half-life (T_{1/2}) will be calculated as 0.693 divided by the elimination rate constant. Standard equations for apparent volume of distribution (Vd/F) and total clearance (Cl/F) will be used²⁰.
- d. Natural immune response evaluation: anti-SARS-CoV-2 antibody titers between days 60-120, stratified by age groups (1 month to 5 years; 5-12 years; 12-18 years). These data will be used to test whether there is endogenous (host) antibody production against SARS-CoV-2. The assumption is that by days 60-120, the levels of exogenously administered antibodies (via convalescent plasma) would have decayed, and high titers at this time point would be suggestive of endogenous antibody production.

6. RISKS AND BENEFITS ASSOCIATED WITH THE STUDY PLAN

6.1 Potential Benefits of Treatment

The potential benefits of treatment with anti-SARS-CoV-2 plasma in children at high-risk for developing COVID-19 due to a high-risk exposure with another individual with COVID-19 are unknown. However, it is anticipated that treatment will decrease the risk of developing symptomatic disease and decrease the severity of illness should it develop. The benefits of anti-SARS-CoV-2 plasma in children with COVID-19 is also still unknown. Preliminary data from adult COVID-19 patients treated with anti-SARS-CoV-2 plasma suggest it can reduce symptoms and mortality.

Another potential benefit is societal: If the frequency with which exposed persons become infected decreases, the risk of further transmission might be reduced, and the epidemic slowed. Childhood outbreaks may drive larger, population-wide outbreaks. *Young children, including asymptomatic children¹⁸, especially those in daycare or preschool, are likely to infect other children. This would not only be a risk to children with certain underlying conditions (see definition of high-risk children in section 3.1), but also to close- or household-contacts (e.g. ≥65-year-old grandparents, caregivers) of these children.* Therefore, until proven therapeutics or vaccines are available, prophylaxis (and social distancing) may remain as the only method to control these outbreaks and prevent infections of high-risk individuals.

Finally, these proposed studies will also provide important data for immunoglobulin-based treatments (that are likely to be developed in the near future) to prevent or treat COVID-19.

6.2 Potential Benefits of Clinical Monitoring and Virologic Testing:

Subjects enrolled in the study will undergo close clinical and virologic monitoring that could facilitate earlier diagnosis of development of COVID-19 with associated benefit to the individual, their family, and the community at large.

6.3 Potential Risks:

- Risks of plasma: It should be noted that many high-risk children (defined in section 3.1 above) already receive blood products for their routine clinical care. The risks from the proposed plasma infusion include fever, chills, rash, headache, serious allergic reactions, transfusion-related acute lung injury, transfusion-associated circulatory overload, and transmission of infectious agents.
- It is also possible that subjects treated with plasma may not develop their own (robust) immunity against SARS-CoV-2
- Children receiving convalescent plasma will be required to postpone administration of live-attenuated vaccines. Given 10 mg/ml of total IgG in plasma, an infusion of 5ml/kg results in a total of 50 mg IgG/Kg, for which a 6 months delay in live-attenuated vaccination is recommended⁵. This specifically regards children between 12-15 months and between 4 to 6 years getting the MMRV vaccine^{5,26}.
- The theoretical risk involves the phenomenon of antibody-mediated enhancement of infection (ADE) which can occur for several viral diseases and involves an enhancement of disease in the presence of certain antibodies. Since the proposed use of convalescent plasma rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE may be unlikely
- Risks of phlebotomy: local discomfort, bruising, hematoma, bleeding, and fainting
- Risks of oropharyngeal and throat swab: local discomfort and vomiting

6.4 Alternatives

The alternative to participation in this study is routine care and monitoring following exposure with an individual with COVID-19 or supportive care for those infected with COVID-19.

6.5 Safety Measures

- Safety Evaluations will assess for the safety of high titer anti-SARS-CoV-2 plasma
- Clinical evaluations: vital signs and symptom screen
- Laboratory evaluations
- Safety laboratory tests (ABO typing, pregnancy testing, CBC and comprehensive metabolic panel) will be performed at the local Clinical Laboratory Improvement Amendment of 1988 (CLIA)-certified clinical laboratory on screening.

6.6 Adverse Event (AE)

Unanticipated problems or events and study deviations will be reported to the JHM-IRB and the FDA, according to the currently published policies of these entities.

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through laboratory test or other means, will be collected and recorded and followed as appropriate. Safety assessments will consist of monitoring and recording all adverse events (AEs), as per the FDA guidelines, IND application sponsors are required to notify FDA in a written safety report of any:

- Adverse experience associated with the use of the drug that is both serious and unexpected OR
- Findings from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, and carcinogenicity.

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is

evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or suspected adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND application.

Serious adverse event or suspected adverse reaction refers to an event or reaction that, in the view of either the investigator or sponsor, results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly or birth defect.

Life-threatening adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or research subject and may require medical or surgical intervention to prevent one of the outcomes listed as serious.

Mandatory Safety Reporting

- **Initial reporting:** IND application sponsor must report any suspected adverse reaction or adverse reaction to study treatment that is both serious and unexpected. Unexpected serious suspected adverse reactions suggesting significant risk to human subjects must be reported to FDA as soon as possible but no later than within 15 calendar days following the sponsor's initial receipt of the information. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported to FDA as soon as possible but no later than 7 calendar days following the sponsor's initial receipt of the information.
- **Follow-up reporting:** Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report. Such report should be submitted without delay, as soon as the information is available but no later than 15 calendar days after the sponsor receives the information.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The type of report (initial or follow-up) should be checked in the respective boxes on Forms 3500A and 1571.

The submission must be identified as:

- "IND safety report" for 15-day reports, or
- "7-day IND safety report" for unexpected fatal or life-threatening suspected adverse reaction reports, or
- "Follow-up IND safety report" for follow-up information.

The report must be submitted to an appropriate Review division that has the responsibility to review the IND application under which the safety report is submitted. Each submission to this IND must be provided in triplicate (original plus two copies).

6.7 Reporting Interval

All AEs and SAEs will be documented from the time of the first administration of study drug (Human Convalescent Plasma) until 30 days after the last dose of study drug.

Ongoing adverse events thought to be related to Human Convalescent Plasma will be followed until resolution of the adverse event, until an alternate cause has been identified, the study participant is lost to follow-up, the study participant withdraws consent, or it has been determined that Human Convalescent Plasma is not the cause of the adverse event.

Resolution of an AE is defined as the return to pre-treatment status or stabilization of the condition with the expectation that it will remain chronic.

Study participants will be followed until the later of either 30 days after the last dose of study drug or until resolution/stabilization of any ongoing drug-related AEs. This follow-up may be obtained in person or by telephone contact.

6.8 Investigator's Assessment of Adverse Events (AE)

The determination of seriousness, severity, and causality will be made by an on-site investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This includes but is not limited to physicians, physician assistants, and nurse practitioners.

Clinically significant abnormal laboratory results would be repeated as soon as possible and followed up as per standard clinical practice. Clinically significant abnormal laboratory results will be reported as AEs.

6.9 Assessment of Association

The association assessment categories that will be used for this study are:

- a. Associated: the event is temporally related to the administration of the study plasma, and no other etiology explains the event.
- b. Not Associated: the event is temporally independent of the study product and/or the event appears to be explained by another etiology.

The investigator must provide an assessment of association or relationship of AEs to the study product based on:

- Temporal relationship of the event to the administration of study plasma
- Whether an alternative etiology has been identified
- Biological plausibility
- Existing therapy and/or concomitant medications

7. SAFETY OVERSIGHT

7.1 Monitoring Plan

All adverse events will be reported to the JHM-IRB according to the current policy statement. The principal investigator is responsible for monitoring and oversight of problems / events.

Scheduled meetings will take place monthly and will include the protocol's principal investigator, data manager, and, when appropriate, the collaborators, and sub-investigators involved with the conduct of the protocol. During these meetings, the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for study objectives.

The principal investigator is responsible for internally monitoring the study. Data must be reviewed to assure the validity of data, as well as the safety of the subjects. The principal investigator will also monitor the progress of the trial, review safety reports, and clinical trial endpoints and to confirm that the safety outcomes favor continuation of the study.

The principal investigator will be the medical monitor for this study. The medical monitor will make an assessment regarding the safety of continuing or modifying the study.

7.2 Data Management

Source documentation will be maintained by site study staff to support the patient research record.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Every effort will be made to maintain the anonymity and confidentiality of all patients during this clinical study. However, because of the experimental nature of this investigational product, the Investigator agrees to allow the IRB, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study site records of all participants enrolled into this study.

The Investigator will assure that each participant's anonymity will be strictly maintained and that each participant's identity is protected from unauthorized parties.

Participants will be assigned a numerical code by the study team. The code list is kept secure and confidential by the study team on physically secured servers. Sufficient information will be retained at the study site to permit sample data and data to be connected with the unique participant number assigned to each study participant.

Data security will be controlled through appropriate restriction of access to only individual users to accomplish their roles in the data management process.

7.3 Halting Criteria for the Study

The study enrollment and dosing will be stopped, and an ad hoc review will be performed if any of the specific following events occur or, if in the judgment of the study physician, subject safety is at risk of being compromised:

- a. Unexpected death of a dosed subject in relation to infusion
- b. Occurrence of a life-threatening allergic / hypersensitivity reaction (anaphylaxis), manifested by bronchospasm with or without urticaria or angioedema requiring hemodynamic support with pressor medications or mechanical ventilation.
- c. Any other event(s) which is considered to be a serious adverse event in the good clinical judgment of the responsible physician. This will be appropriately documented.

7.3.1 Halting Criteria / Rules for Discontinuing Infusion

Infusion of study plasma will be halted if any of the following manifestations of anaphylaxis develop and will not be restarted:

- a. Skin or mucous membrane manifestations: hives, pruritus, flushing, swollen lips, tongue or uvula
- b. Respiratory compromise: dyspnea, wheezing, stridor, hypoxemia
- c. Hypotension, tachycardia or bradycardia defined for the subject's age^{27,28}
- d. Syncope
- e. Confusion
- f. Any other symptom or sign which in the good clinical judgment of the study clinician or supervising physician warrants halting the infusion. For example, the rapid onset of gastrointestinal symptoms, such as nausea, vomiting, diarrhea, and cramps, for instance, may be manifestations of anaphylaxis and may warrant an immediate halt prior to meeting full SAE criteria.

8. ETHICS/PROTECTION OF HUMAN SUBJECTS

8.1 Ethical Standard

The JHU is committed to the integrity and quality of the clinical studies it coordinates and implements. JHU will ensure that the legal and ethical obligations associated with the conduct of clinical research involving human subjects are met. The information provided in this section relates to all JHU sites participating in this research study.

As the Department of Health and Human Services continues to strengthen procedures for human subjects' protections via new regulations, JHU will review these evolving standards in relation to the proposed activities and will advise the investigators on those that may apply.

In addition, JHU has a Federal wide Assurance (FWA) number on file with the Office for Human Research Protections (OHRP). The FWA number for JHU is FWA00005834.

This assurance commits a research facility to conduct all human subjects' research in accordance with the ethical principles in The Belmont Report and any other ethical standards recognized by OHRP. Finally, per OHRP regulations, the research facility will ensure that the mandatory renewal of this assurance occurs at the times specified in the regulations.

8.2 Institutional Review Board

The JHU IRB will review this protocol and all protocol-related documents and procedures as required by OHRP and local requirements before subject enrollment. The JHU IRB currently holds and will maintain a US FWA issued by OHRP for the entirety of this study.

8.3 Informed Consent Process

The informed consent process will be initiated before an individual or their legal representatives agrees to participate in the study and should continue throughout the individual's study participation. Subjects or their legal representatives must have the ability to read, understand and provide written informed consent for the initiation of any study related procedures. The subject or their legal representatives will sign the informed consent document before any procedures are undertaken for the study. A copy of the signed informed consent document will be given to the subject or their legal representatives, for their records. The consent will explain that subjects or their legal representatives may withdraw consent at any time throughout the course of the trial. Extensive explanation and discussion of risks and possible benefits of this investigation will be provided in understandable language. Adequate time will be provided to ensure that the subject or their legal representatives has time to consider and discuss participation in the protocol.

The consent will describe in detail the study interventions / products / procedures and risks / benefits associated with participation in the study. The rights and welfare of the subjects will be protected by emphasizing that their access to and the quality of medical care will not be adversely affected if they decline to participate in this study. *We will plan initial consent process done via video chat prior to subjects coming to JHH in order to minimize face-face time with study personnel at the screening visit. Currently, we will not be taking paper copies of consent outside of COVID-19 positive patient rooms.*

8.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsors and their agents. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. Having said that, de-identified data would be shared with a registry held by Children's National Hospital (P.I. Cyril Jacquot), provided the protocol would be approved within a separate application (IRB00259740). The results of the research study may be published, but subjects' names or identifiers will not be revealed. Records will remain confidential. To maintain confidentiality, the PI will be responsible for keeping records in a locked area and results of tests coded to prevent association with subjects' names. Data entered into computerized files will be accessible only by

authorized personnel directly involved with the study and will be coded. Subjects' records will be available to the FDA, the NIH, the manufacturer of the study product and their representatives, investigators at the site involved with the study, and the IRB.

8.5 Future Use of Stored Specimens

Subjects will be asked for consent to use their samples for future testing before the sample is obtained. The confidentiality of the subject will be maintained. There will be no plans to re-contact them for consent or to inform them of results. The risk of collection of the sample will be the small risk of bruising or fainting associated with phlebotomy, however these samples will be taken at the same time as other protocol required samples.

No human genetic testing will be performed on the samples.

Blood samples will be collected at 2 or more time points (see Schedule of Events). Serum will be frozen in 500 uL aliquots. These samples will be used to answer questions that may arise while the study is underway or after it is completed. If, for instance, there were unanticipated AEs, serum could be used to run tests that might help determine the reason for the adverse events. Cytokines could be measured, for example.

Samples would not be shared with investigators other than investigators at JHU unless outside investigators had relevant assays or expertise not available to the study investigators. The specimens would remain linked and at JHU for 5 years. Any use of these specimens not specified in the current protocol will be reviewed by the JHU IRB.

8.6 Record Retention

The site investigator is responsible for retaining all essential documents listed in the ICH GCP Guidelines. The FDA requires study records to be retained for up to 2 years after marketing approval or disapproval (21 CFR 312.62), or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational agent for a specific indication. These records are also to be maintained in compliance with IRB / IEC, state, and federal medical records retention requirements, whichever is longest. All stored records are to be kept confidential to the extent provided by federal, state, and local law. It is the site investigator's responsibility to retain copies of source documents until receipt of written notification to the sponsor.

No study document would be destroyed without prior written agreement between the sponsor and the Principal Investigator. Should the investigator wish to assign the study records to another party and/or move them to another location, the investigator must provide written notification of such intent to sponsor with the name of the person who will accept responsibility for the transferred records and/or their new location. The sponsor must be notified in writing and written permission must be received by the site prior to destruction or relocation of research records.

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