PROTOCOL TITLE: Therapeutic plasma exchange for COVID-19-associated hyperviscosity

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1. Study Summary

Study Title	Therapeutic plasma exchange for COVID-19-associated hyperviscosity
Study Design	Phase 1 Randomized Controlled Trial
Primary Objective	1. Evaluate change in plasma viscosity after TPE with FP vs SOC in COVID-19 patients. 2. Evaluate safety and tolerability of TPE with FP vs SOC in COVID-19 patients.
Secondary Objective(s)	Compare outcomes of TPE vs SOC for the following measures: 1. Mortality 2. Bleeding/thromboembolic complications 3. Duration of ICU stay 4. Total time to hospital discharge 5. Clinical and laboratory evaluation
Research Intervention(s)/Interactions	Study participants will be randomized 1:1 to the following arms: 1. Intervention: 2 treatments of TPE with FP replacement 2. Control: SOC with ability to receive TPE if clinically indicated due to failure of SOC (plasma viscosity > 3.5 cp or candidate for TPE as salvage therapy as assessed by clinical team)
Study Population	Critically ill COVID-19 patients with hyperviscosity or hyperfibrinogenemia admitted to the ICU
Sample Size	20
Study Duration for individual participants	From time of randomization until death or hospital discharge
Study Specific Abbreviations/ Definitions	COVID-19 (disease caused by SARS-CoV-2 virus) Therapeutic plasma exchange (TPE) Frozen plasma (FP) von Willebrand factor (vWF) Standard of Care (SOC)
Funding Source (if any)	Department of Pathology and Laboratory Medicine

2. Objectives

Critically ill COVID-19 patients have high rates of complications, including respiratory failure, renal impairment, and a coagulopathic state that may exacerbate these conditions and contribute to additional end organ injury.[1] Consistent with a

fundamentally distinct nature of COVID-19-associated disease, our preliminary studies demonstrate that patients with COVID-19 exhibit an increase in plasma viscosity. Furthermore, we have found that plasma viscosity strongly correlates with sequential organ failure assessment (SOFA) scores, a mortality prediction score used in the ICU, in COVID-19 infected patients. These results strongly suggest that altered blood flow secondary to hyperviscosity may contribute to end organ injury and therefore morbidity and mortality in the most critically ill COVID-19 patients. More detailed analysis of the potential etiology of COVID-19-associated plasma hyperviscosity has demonstrated that these patients also have significantly elevated levels of the plasma protein fibrinogen. Increased fibrinogen levels, which may be either entirely responsible for or at least contribute to hyperviscosity in these patients, may be the primary mediator of refractory hypercoagulability in this patient population. Thus, hyperviscosity induced by hyperfibrinogenemia may be a critical driver of morbidity and mortality in patients with COVID-19.

Therapeutic plasma exchange (TPE) is the only procedure known to directly and rapidly decrease plasma viscosity, suggesting that TPE may improve patient outcomes in critically ill patients with COVID-19 by decreasing plasma viscosity and thereby enhancing blood flow. However, as a procedure, extensive implementation of TPE would require significant devotion of hospital resources, including apheresis machines and the staff needed to successfully conduct these procedures. The procedures alone require staff to have prolonged interactions with critically ill COVID-19 patients, placing them at a potentially increased risk for contracting COVID-19. Preliminary observational data suggest that TPE may be beneficial to COVID-19 patients, with five of seven patients treated thus far within Emory Healthcare-affiliated institutions showing signs of improvement as measured by plasma viscosity and SOFA scores. These results are promising. However, significant equipoise exists among treating physicians. Given the unknown benefit of TPE for patients with COVID-19 within Emory Healthcare, it is currently not possible to adequately weigh risks and benefits of this procedure. It is therefore essential that clear and unequivocal data be generated in order to accurately assess the risk and benefits of this procedure for both patients *and* staff. Such data will also aid in determining the necessary resources that may be needed to successfully conduct TPE for this patient population.

In order to clearly assess the potential benefit of TPE for COVID-19 and therefore more accurately define the risks and benefits of this procedure for both patients *and* staff, the overall objective of this study is to define the impact of therapeutic plasma exchange (TPE) on hyperviscosity and patient outcomes in COVID-19 patients. TPE is the only direct treatment for acute hyperviscosity[2], although its role in COVID-19 management has not yet been established. To date, seven COVID-19 patients with hyperviscosity and hyperfibrinogenemia have been treated with TPE in the Emory Healthcare system (EHC), with several patients appearing to benefit from this procedure. However, a more formal and deliberate approach to determining whether TPE reduces viscosity and results in beneficial outcomes in these patients is needed. We hypothesize that TPE will normalize plasma viscosity while also reducing the level of key factors such as fibrinogen and

proinflammatory cytokines (tumor necrosis factor [TNF], IL-6, and IL-1β) that likely drive inflammation and thrombophilia, which leads to clot formation, in these patients. In doing so, we hypothesize that TPE will lead to improved clinical outcomes in critically ill COVID-19 patients compared to those receiving standard of care (SOC).

Primary Objectives

1. Evaluate change in plasma viscosity after TPE vs SOC in critically ill COVID-19 patients.
2. Evaluate safety and tolerability of TPE vs SOC in critically ill COVID-19 patients.

Secondary Objectives

Compare outcomes of TPE vs SOC for the following measures:

1. Mortality
2. Bleeding/thromboembolic complications
3. Requirement for major forms of supportive care (mechanical ventilation, RRT, etc.)
4. Time to treatment failure
5. Duration of ICU stay
6. Total time to hospital discharge
7. Clinical and laboratory evaluation, by system

3. Background

The COVID-19 pandemic caused by the SARS-CoV-2 virus can cause a spectrum of disease ranging from asymptomatic/mild pneumonia in 80% of patients, to critical illness (respiratory failure, septic shock and/or multiple organ dysfunction/failure) in 5% of patients[3]. However, it has been a challenge to decipher the cause of severe COVID-19-related complications and therefore define optimal approaches to treat critically ill patients with COVID-19, particularly those with signs of severe organ injury that often develop multi-organ failure.

In a preliminary study analyzing various laboratory markers in COVID-19 patients that may contribute to inadequate blood flow and therefore compromised organ function, we observed elevated plasma viscosity measurements ranging from 1.9-4.2 centipoise (cp, normal range is 1.4-1.8 cp) in 15 critically ill patients[4]. These results suggest that altered blood flow secondary to hyperviscosity may directly alter blood flow, contributing to end organ injury and possibly death. In these cases of severe COVID-19, hyperviscosity was strongly correlated with higher Sequential Organ Failure Assessment (SOFA) scores, a measure of mortality risk and level of organ dysfunction in ICU patients (Pearson $r = 0.841$, $R2 = 0.7072$, $p<0.001$)[4].

In addition to directly impacting end organ injury secondary to altered blood flow, we hypothesize that increased viscosity due to hyperfibrinogenemia contributes to increased thrombotic complications in these patients. Notably, all four of the initial patients evaluated with plasma viscosity >3.5 cp had a known acute thrombotic complication. Hyperviscosity is a risk factor for thrombosis[5] by inducing venous stasis

and endothelial damage. Alternatively, hyperviscosity may serve as a biomarker reflecting the patient's hypercoagulable state. Multiple studies have suggested a high rate of thromboembolic complications (DVT, PE, limb ischemia, clotting of venous catheters) in critically ill COVID-19 patients[6], even in the setting of VTE prophylaxis[7–12]. Anticoagulation treatment has been shown to decrease mortality in critically ill COVID-19 patients[13], and many institutions, including our own, have developed VTE prophylaxis and treatment guidelines for use in patients with COVID-19. Many of the critically ill COVID-19 patients meet ISTH criteria for disseminated intravascular coagulation (DIC)[14], but the exact nature and mechanism driving this COVID-19 associated coagulopathy remains unknown[15]. However, despite these measures, many patients remain refractory to VTE prophylaxis, suggesting that a fundamentally distinct nature of the COVID-19 thrombophilic state. Given the potential contribution and fundamentally unique nature of hyperviscosity and high fibrinogen levels in the occurrence of thrombotic events, these variables may reflect a key component of end organ injury and refractory thrombotic complications driving disease outcomes in critically ill COVID-19 patients.

TPE is indicated for treatment of hyperviscosity syndrome in hypergammaglobulinemia, most commonly seen in Waldenstrom macroglobulinemia and multiple myeloma[2]. To date, there have been seven critically ill COVID-19 patients at Emory with hyperviscosity accompanied by refractory hypercoagulability that have undergone TPE using frozen plasma (FP) as the replacement fluid. Refractory hypercoagulability in these patients was defined as arterial/venous thrombosis or worsening/refractory organ failure suspected to be due to microthrombi while on therapeutic anticoagulation. The initial 4 patients from EUHM had plasma viscosity >3.5 cp and SOFA scores >14, while 2 patients from ESJH and 1 patient from EUH had values <3.5 cp and SOFA scores <14. All patients had significant normalization in plasma viscosity after 2-3 treatments of TPE. Five patients had clinical improvement reflected by a favorable change in SOFA scores. Two patients, who were some of the first treated, were initiated on TPE as salvage therapy. They had very high SOFA scores (19, and 15) pre-treatment and despite use of TPE, these patients unfortunately succumbed to COVID-19. Of note, mortality in patients with SOFA scores over 11 has been reported to be over 80%[16].

Although only limited conclusions can be drawn from this small sample size, our initial experience has suggested that early intervention with TPE prior to significant and perhaps irreversible end-organ injury may not only reduce plasma viscosity, but also improve clinical outcomes in COVID-19 patients. We therefore hypothesize that early normalization of plasma viscosity through TPE with FP replacement will improve clinical outcomes in critically ill COVID-19 patients with hyperviscosity by restoring end organ blood flow and reducing the likelihood of refractory hypercoagulability.

4. Study Endpoints

Primary Study Endpoints:

Difference in plasma viscosity measured within 24 hours before TPE and within 24 hours after second TPE treatment.

Primary Safety Endpoints:
Cumulative incidence of adverse events directly associated with TPE during the study period as determined by clinical judgment of ICU team providing direct patient care and the study PI.

Secondary Study Endpoints:
Compare clinical outcomes of TPE with FP replacement vs SOC on the following measures:

1. Clinical outcomes at 3, 7, 14, and 28 days after final TPE treatment:
    a. All-cause mortality
    b. Bleeding/Thromboembolic complications – Any acute bleeding requiring transfusion support, VTE (DVT/PE), Arterial (MI, stroke, limb ischemia), RRT/line clots
    c. Time to treatment failure – Plasma viscosity > 3.5 cp and/or candidate for TPE as salvage therapy as assessed by clinical team
    d. Duration of ICU stay/hospitalization
    e. Discharge disposition - home/LTAC vs palliative/death
2. Evaluation of daily clinical and repeated laboratory parameters:
    a. Clinical status based on a modified WHO ordinal scale. The 12-point ordinal scale consists of the following categories:
        1) No clinical or virological evidence of infection
        2) Evidence of infection but no limitation of activities
        3) Limitation of activities
        4) Hospitalized, no oxygen therapy
        5) Oxygen by mask or nasal prongs
        6) Non-invasive ventilation or high-flow oxygen
        7) 1 major form of supportive care or evidence of thrombotic disease (Intubation and mechanical ventilation or ECMO or RRT or pressor support or evidence thromboembolic disease (e.g. clotting of RRT, ECMO, DVT, PE, MI, stroke, ischemic limb, etc.)
        8) 2 major forms of supportive care and/or evidence of thrombotic disease (Intubation and mechanical ventilation or ECMO or RRT or pressor support or evidence thromboembolic disease (e.g. clotting of RRT, ECMO, DVT, PE, MI, stroke, ischemic limb, etc.)
        9) 3 major forms of supportive care and/or evidence of thrombotic disease (Intubation and mechanical ventilation or ECMO or RRT or pressor support or evidence thromboembolic disease (e.g. clotting of RRT, ECMO, DVT, PE, MI, stroke, ischemic limb, etc.)
        10) 4 major form of supportive care and/or evidence of thrombotic disease (Intubation and mechanical ventilation or ECMO or RRT or pressor support or

evidence thromboembolic disease (e.g. clotting of RRT, ECMO, DVT, PE, MI, stroke, ischemic limb, etc.)

11) 5 major form of supportive care and/or evidence of thrombotic disease (Intubation and mechanical ventilation or ECMO or RRT or pressor support or evidence thromboembolic disease (e.g. clotting of RRT, ECMO, DVT, PE, MI, stroke, ischemic limb, etc.)
12) Death

b. Clinical assessment – Vital signs, physical examination, degree of supportive care (vent settings, vasopressor requirements, need for RRT), clinical scoring tools (SOFA, PaO2/FiO2 ratio, Ventilatory ratio)
c. Laboratory evaluation – CBC, CMP, inflammatory and coagulation parameters

5. Study Intervention/Investigational Agent

The study intervention being evaluated is TPE with FP replacement. In the TPE with FP arm, participants will receive 2 treatments of TPE with FP replacement on two sequential days. All procedures will be performed by the apheresis staff at the respective hospital sites (EUH, EUHM, ESJH) following institutional SOP. FP will be obtained from American Red Cross or LifeSouth Community Blood centers. ABO typing and infectious agent screening (Hepatitis B, Hepatitis C, HIV-1, HIV-2, Human T-Lymphotropic Virus Types I & II, Babesia, Trypanosoma cruzi, West Nile Virus (WNV), Zika) will be performed per standard blood banking protocol.

6. Procedures Involved

COVID-19 infected patients admitted to the ICU will be assessed for study inclusion. Plasma viscosity and fibrinogen will be measured as part of routine clinical care. Eligibility for enrollment will be determined by the patient's clinical team.

Subjects will be randomized (Day 1) in a 1:1 ratio to receive TPE with FP vs SOC. Randomization will be conducted by web-based tool that will pre-generate all treatment assignments. The assignment list will be maintained by designated staff independent from study and sent to the PI/research team for each eligible participant.

In the TPE with FP arm, participants will receive 2 treatments of TPE with FP on sequential days (Day 2 and 3). All procedures will be performed by Transfusion Medicine staff at their respective hospital sites (EUH, EUHM, ESJH) following institutional SOP. Participants will continue to receive SOC and be closely monitored by ICU team for any change in clinical status, and any adverse events directly related to study intervention will be reported to PI. Plasma viscosity will be measured within 24 hours before TPE (Day 1 or 2) and within 24 hours following the second TPE treatment (Day 3 or 4). Additional laboratory parameters will be acquired in parallel as per standard management. Medical records of the study participants will be reviewed to obtain clinical data including physician records, hospital records, clinical records, and laboratory results. At any point during study period after the second TPE treatment, if

plasma viscosity > 3.5 cp or if clinical condition worsens to a point that warrants TPE as salvage therapy based on best clinical judgment of ICU team, participants will be considered to be in treatment failure and offered additional TPE as part of their SOC. Patients in whom this happens will still be followed for outcome measurements.

In the SOC arm, participants will not receive TPE with FP, but continue to receive SOC and be closely monitored by ICU team for any change in clinical status. Plasma viscosity will be measured on Day 1 and Day 3. Additional laboratory parameters will be acquired in parallel as per standard management. Medical records of the study participants will be reviewed to obtain clinical data including physician records, hospital records, clinical records, and laboratory results. At any point during study period, if plasma viscosity > 3.5 cp or if clinical condition worsens to a point that warrants TPE as salvage therapy based on best clinical judgment of ICU team, participants will be considered as treatment failure and offered TPE as part of their SOC. Patients in whom this happens will still be followed for outcome measurements.

7. Data and Specimen Banking

Discarded clinical specimens collected as part of routine clinical care of participants during study period, along with discarded apheresed patient plasma, will be collected and stored in PI's laboratory for future research studies. These include discarded clinical specimens prior to and after each TPE treatment, but no additional specimens will be collected for non-clinical research purposes only. Data will be deidentified and coded to remove identifying information. An electronic key linking the patient identifiers with the sample ID will be maintained on access-restricted Emory server and restricted to the study PI and co-investigators.

8. Sharing of Results with Participants

Clinical data will be entered into patient medical records, and study participants will be able to request them through the medical records office at their respective hospital. Study results will be made available as publication.

9. Study Timelines

- The duration of an individual participant's participation in the study is for the duration of their hospitalization.
- The duration anticipated to enroll all study participants:
  Estimated completion in 6 months from start of study date (November 2020), but depends on the number of COVID-19 patient admissions, which remains uncertain. The timeline may be extended through winter 2021 as needed.
- The estimated date for the investigators to complete this study (complete primary analyses):
  12 months from completion of study date (November 2021), but timeline may be extended as needed depending on study completion date.

10. Inclusion and Exclusion Criteria

COVID-19 infected patients admitted to the ICU will be enrolled in the study. Plasma viscosity and fibrinogen will be measured as part of routine clinical care. Eligibility will be determined by the patient's clinical team.

Inclusion Criteria:

1. Age ≥ 18 years
2. Patients admitted to the ICU at EUH, EUHM or ESJH
3. Evidence of COVID-19 infection documented by a laboratory test either by:
    a. A diagnostic test (e.g., nasopharyngeal swab, tracheal aspirate, other) OR
    b. Positive serological test for SARS-CoV-2 antibodies OR
    c. Medical records from outside institution
4. Plasma viscosity ≥2.3 and ≤3.5 centipoise (cp) OR Fibrinogen >800 mg/dL

Exclusion Criteria:

1. Patients with plasma viscosity > 3.5 cp
2. Moribund patients that the ICU clinical team expects to die within 24 hrs
3. Patients with any condition that, in the opinion of the clinical team or investigator, could increase the subject's risk by participating in the study or confound the outcome of the study
4. Patients participating in another clinical trial that prohibits the use of TPE
5. Pregnant women
6. Prisoners

Community Participation:
NA

11. Vulnerable Populations

Critically ill patients may be cognitively impaired due to severity of their illness. See attached HRP-417 form.

12. Local Number of Participants

We plan to enroll a total of 20 patients. Based on experience, we estimate that 50% of critical care admissions at EUH, EUHM, ESJH with COVID-19 will meet enrollment criteria.

13. Recruitment Methods

EUH, EUHM, and ESJH clinicians providing direct care for COVID-19 patients admitted to the EHC ICUs will screen patients for eligibility based on clinical and laboratory

information obtained as part of routine SOC. Investigators will be notified of eligible patients, and will consent patient or appropriate medical decision maker for enrollment in study. Study participants will not be given any form of payment or reimbursed for expenses/travel.

14. Withdrawal of Participants

Participant or appropriate medical decision maker may provide written notice to formally withdraw from study. In the event of formal withdrawal from study, any specimen collected and stored as part of study will be discarded. However, other clinical specimen may still be collected as part of providing routine SOC. The intervention arm of this study involves 2 treatments of TPE. If participant declines TPE but consents to continued data collection, we will crossover participant to the SOC comparator arm of this study. If participant undergoes at least 1 session of TPE but consents to continued data collection, they will remain in the intervention arm of this study.

15. Risks to Participants

All participants in this study are critically ill with COVID-19 and require ICU admission. Such patients experience frequent complications and events that can cause deterioration in function of any and all vital organs. Specific risks associated with this research protocol are limited to possible complications related to apheresis/transfusion procedure that the TPE group will receive, as opposed to the SOC group. The following are known complications associated with all apheresis/transfusions regardless of indication:

- Hypotension
- Hypocalcemia
- Citrate Toxicity
- ACE Inhibitor Reactions
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Transfusion-associated dyspnea (TAD)
- Allergic reaction (where severity can range from mild to life threatening and rarely death)
- Hypotensive transfusion reaction
- Febrile non-hemolytic transfusion reaction (FNHTR)
- Acute hemolytic transfusion reaction (AHTR)
- Delayed hemolytic transfusion reaction (DHTR)
- Transfusion-transmitted infection (TTI)

While we do not anticipate that the relative risks will fundamentally differ, these risks are actively disclosed to patients as part of the routine consent process. Minor/mild

reactions (hypotension, hypocalcemia, allergic) are not uncommon, whereas others occur in <1% of procedures (citrate toxicity), or are extremely rare (hemolytic transfusion reactions). TPE is performed by trained nurses who are well-versed in recognizing these known complications and following protocols that include mitigation strategies for potential side effects.

No potential risks are foreseen to be associated with any of the testing, as it will be conducted on samples from the unit collected as part of routine care.

16. Potential Benefits to Participants

Study participants may directly benefit from preventing/mitigating thromboembolic complications, and improvement in clinical outcome (organ function, enhanced probability of survival, shortened time to recovery).

17. Data Management and Confidentiality

Data Analysis

Sample size and power considerations: The primary efficacy outcome for the two parallel group clinical trial is plasma viscosity. Sample size and power considerations for the primary outcome, plasma viscosity, were based on longitudinal data (before and after PLEX treatment) from 7 patients (mean = 3.4 and 1.6 centipoise before and after PLEX treatment; standard deviation = 0.69 and 0.15 centipoise before and after PLEX treatment). The primary goal of the trial is to compare the change across time in the PLEX arm to the change across time in the standard of care arm. Group sample sizes of 10 in the PLEX arm and 10 subjects in the standard of care arm achieve 93% power to detect a difference in mean change between treatment groups of 1.0 centipoise in a design with pre/post measurements. These power calculations for plasma viscosity change assume a 1.5 centipoise improvement (decline) on average between baseline and after PLEX treatment and 0.5 centipoise improvement on average in the standard of care group. This sample size calculation assumes the estimated standard deviation of the differences of 0.61 centipoise and the correlation between paired plasma viscosity measurements on the same subject of 0.60. The significance level (alpha) is 0.05 using a two-sided, two-sample t-test. If the estimated standard deviation of the differences is as high as 0.75, the power will be 80%. All plasma viscosity power calculations were done with PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

Statistical Analysis Plan: The primary analyses of the data will be performed according to subjects' original treatment assignment (i.e., intention-to- treat analyses) regardless of compliance to treatment and the inclusion of all data from all subjects randomized in the final analysis. The primary endpoint in this intent-to-treat, parallel-group trial will be mean plasma viscosity. A repeated-measures analysis of plasma viscosity will be performed with a means model via the SAS MIXED Procedure (version 9.4; SAS Institute, Cary, NC), providing separate

estimates of mean plasma viscosity by time on study (before and after treatment) and treatment group.

The model will include three predictors [treatment arm, time on study (categorical) and the statistical interaction between treatment arm and time on study]. A compound-symmetric variance-covariance form in repeated measurements will be assumed for plasma viscosity and robust estimates of the standard errors of parameters will be used to perform statistical tests construct 95% confidence intervals[17]. The model-based means are unbiased with unbalanced and missing data, as long as the missing data are non-informative (missing at random, MAR). A P-value ≤0.05 will be considered statistically significant for the main effects (treatment and time on study) and for the treatment by time on study interaction effect from the repeated-measures analysis. **The statistical test for interaction between time on study and treatment will be the overall hypothesis test to determine whether plasma viscosity in the two study groups changed in significantly different ways during follow-up (i.e., different temporal patterns over time).** If mean plasma viscosity in the two treatment groups is consistently different or similar over time (i.e., no statistical interaction) then the main effect test for treatment will be used as the primary hypothesis test to compare the 2 treatment groups. The primary study results from this model will be the mean plasma viscosity and 95% confidence interval for the PLEX group, the mean plasma viscosity and 95% confidence interval for the standard of care group and the mean difference and 95% confidence interval. If a significant interaction is detected, then t-tests will be used to compare the differences between the model-based treatment means at each time point and to compare differences over time within each treatment arm. Specific statistical tests will be done within the framework of the mixed effects linear model. All statistical tests will be 2-sided and unadjusted for multiple comparisons. Secondary outcomes for additional laboratory parameters (fibrinogen, d-dimer, CRP, IL-6, and immunoglobulin levels) will be analyzed using the same plan described for plasma viscosity.

This trial will provide important estimates of variability (within-subject and between-subject standard deviation) for plasma viscosity. The estimates of variability will be valuable to power future clinical trials since these variability estimates are essential components for sample size calculations. Due to the small sample sizes, results from these studies will also focus on the magnitude of the differences for each outcome, consistency of findings and clinical significance.

Duration of ICU stay, total time to hospital discharge and time on respiratory support will be compared by treatment group with the Wilcoxon rank-sum test. The assessment for a difference in hospital mortality and bleeding/thromboembolic complications by treatment group will be a two-sided exact chi-square test.

Study Ability to Detect Uncommon Safety Events

Adverse Events (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening

adverse event, inpatient 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/birth defect. The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

All participants in this study are critically ill with COVID-19 and require ICU admission. Such patients experience frequent complications and events that can cause deterioration in function of any and all vital organs. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition appears to deteriorate in response to the procedure it will be recorded as an AE.

The table below addresses safety using adverse event probabilities based on the targeted enrollment of 10 patients in each treatment group. The table provides the binomial probabilities of observing 0, 1+, or 2 or more occurrences of an AE during follow-up.

Adverse Event Probabilities for n=10 PLEX patients or n=10 standard of care patients

Event Rate (AE)	Probability [0 / 10 Events]	Probability [1+ / 10 Events]	Probability [2+ / 10 Events]
5%	0.60	0.40	0.09
10%	0.35	0.65	0.26
15%	0.20	**0.80**	0.46

Thus, we can be **80%** sure of observing at least one episode of a rare AE if the true rate of an AE is 15%.

Adverse Events and Laboratory Toxicities: Each adverse event and each laboratory toxicity will be counted only once per participant as the most severe level reported during follow-up. Tabular summaries of the number of participants reporting each AE, for both treatment-related and unrelated AEs as well as just treatment related AEs, respectively will be reported. Adverse events and grade III or higher laboratory toxicities observed during follow-up will be reported by treatment group.

Data Storage

1. All data will be kept on encrypted and password-secure Emory University Hospital computer systems, encrypted devices that are Emory IT vetted, or secure Emory servers, such as Trusted storage, with only the investigators listed having access to review the data.
2. Data will be deidentified and coded to remove identifying information. An electronic key linking the patient identifiers with the sample ID will be maintained on access-restricted Emory server and restricted to the study PI and co-investigators.
3. Unused data will be destroyed upon completion of the study.
4. The Data will not be reused or disclosed to any other person or entity.

18. Provisions to Monitor the Data to Ensure the Safety of Participants

Participants will be closely monitored by ICU clinical team on 24/7 basis for any change in clinical status, and **any adverse events directly related to study intervention as defined above in Section 15: Risks to Participants** will be reported to PI (Dr. Maier) within 24 hours of occurrence. The role for TPE in hemostatic and hematologic indications are well established[2] and we believe this single-site clinical trial presents only minimal risks.

Scheduled meetings will take place monthly and will include the protocol's principal investigator, co-investigators, research coordinator and, when appropriate, the collaborators and researchers 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, 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 will be reviewed to assure the safety of the subjects as well as the validity of the data. 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 and research coordinator will continually assess the safety of the study and make an assessment regarding the safety of continuing or modifying the study.

Meeting reporting requirements: All adverse events will be collected on each participant. We will report adverse events to the IRB as required by IRB P&P and as part of regular progress reports.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

19. Provisions to Protect the Privacy Interests of Participants

- The research team will take steps to make the participants feel at ease with the research situation in terms of the questions being asked and the procedures being performed.
- The participants will be reassured that no private data will be shared with anyone outside the study and that they have the right to withdraw without fear of penalty at any time prior to, during, or after enrollment.
- The participants will be given an opportunity to as any questions or address any concerns they may have at the time of recruitment or anytime thereafter.
- The research team is permitted to access clinical information from the participant's electronic medical record for data analysis.

20. Economic Burden to Participants

There are no costs that participants will be responsible for because of participation in the research.

21. Consent Process

Consent for study enrollment will be carried out by study co-investigators that are part of the clinical care team. The consent discussion should take approximately ten minutes; however, the discussion will continue as long as is necessary to answer all of the patient's questions. We will minimize coercion or undue influence by emphasizing that the patient has the choice to decline participation and will not be compensated for their time or effort. In order to ensure that the patient understands the process, we will provide time for follow up questions. Consent will be obtained in English, but an

appropriate medical interpreter will be used if the prospective participants do not understand and/or speak English.

Critically ill patients may be unable to consent due to severity of their illness. If subject is unable to consent, the legally authorized representative (LAR) in the following order of priority as outlined in Emory IRB P&P will be sought for consent:

1. Durable power of attorney for health care
2. Court appointed guardian for health care decisions
3. Spouse
4. Any Adult offspring for his/her Parents
5. Any Parent for his/her Adult offspring
6. Any Adult for his/her brother or sister
7. Any grandparent for his/her grandchild
8. Any Adult grandchild for his or her grandparent
9. Any Adult niece, nephew, aunt, or uncle of the patient who is related to the patient in the first degree

In the event that the patient or LAR cannot provide a wet signature in person, the LAR will be able to remotely sign and send the consent via encrypted email.

22. Setting

- The research team will work with clinicians providing direct care to COVID19 patients admitted to the ICU at EUH, EUHM, ESJH to identify and recruit potential study participants.
- TPE will be performed on site where patient is admitted.
- Laboratory specimen collected as part of routine SOC will be processed in accordance to individual hospital laboratory policy.
- Laboratory specimen collected as part of research study will be processed and stored at the PI's laboratory.

23. Resources Available

- EUH, EUHM, and ESJH are all part of Emory Healthcare, which is the largest healthcare system in the state of Georgia. EUH is a large tertiary academic hospital. The study will be a collaborative effort among different laboratories within the three hospitals.
- The ICU census of COVID19 patients at EUH, EUHM, and ESJH has been as high as ~80 patients per day (April 2020). Given the continued pandemic, we anticipate that there will be sufficient volume of COVID19 patients requiring ICU admissions for study enrollment over the recruitment period.
- The study participants will have access to medical and psychological resources offered as part of their clinical care as a patient of the Emory Healthcare system.

Research team and clinicians providing direct care will be available to thoroughly address any questions or concerns regarding participation in this study.

- The research team's time will be spent recruiting study participants, performing chart review, and analyzing data. Other persons at Emory involved in the study will spend their time performing the various assays included in the study (detailed above).
- All co-investigators and all other persons assisting with the project will be adequately informed about the protocol, the research procedures, and their duties and functions prior to recruitment of the first study participant. Additionally, periodic reviews will be held every quarter to ensure all protocols and procedures are being followed.

24. References

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