





SUPPLEMENT ARTICLE

Treating the endotheliopathy of SARS-CoV-2 infection with plasma: Lessons learned from optimized trauma resuscitation with blood products

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1 | BACKGROUND

The novel coronavirus SARS-CoV-2, which causes COVID-19, surfaced in late 2019, and by mid-March 2020 it had been declared a formal pandemic producing a worldwide crisis.¹ The global death toll climbed to above 6000 by March 15, 2020, just a few days after a national emergency was declared in the United States. As testing increased, the crisis escalated, with health officials around the world reporting more than 21,000 new cases on March 19 alone. As of June, 2021 there are 176 million reported cases worldwide and 3.8 million deaths globally, with over 600,000 deaths in the United States alone (Johns Hopkins University Website for COVID-19 <https://coronavirus.jhu.edu/>).

In addition to the devastating pulmonary complications of COVID-19, the disease produces a relatively common syndrome of multi-system derangements and dysfunction that appear separate from the profound respiratory compromise. What have emerged as key components in the pathogenesis and lethality of this syndrome are the cardiac and vascular complications.²⁻⁴ Infection by SARS-CoV-2 can lead to acute respiratory distress syndrome (ARDS), which is associated with a robust cytokine storm, coagulation disturbances, and multi-organ failure (MOF).⁵ It can be hypothesized that systemic vascular injury and inflammation caused by the virus are major drivers behind the disease pathology of SARS-CoV-2 infection, where patients develop ARDS and subsequent MOF, reminiscent of what has been observed in bacterial sepsis or massive hemorrhage.

2 | ENDOTHELIOPATHY OF SARS-COV-2

SARS-CoV-2 utilizes the angiotensin I converting enzyme 2 (ACE2) receptor, which binds to the virus' spike protein.⁵⁻⁷ The ACE2 receptor is widely expressed in the lung alveolar type II cells, endothelial cells, cardiac cells, as well as cells of the liver, kidney, and intestine.^{8, 9} The capability of the virus to infect a wide range of tissues and cell types is likely the cause of the systemic nature of COVID-19, leading to diffuse endothelial compromise and multiple organ failure.⁵ Recent characterization of the virus by Gordon et al. found 29 viral proteins physically interacting with over 300 human proteins based on studies utilizing affinity purification mass spectrometry.¹⁰ Many of these proteins and the open reading frames that code for them are likely pathogenic, and some may be directly injurious to the vascular endothelium.

In a recent correspondence by Varga et al. in *Lancet*, tissue pathology from three infected patients demonstrated involvement of the virus in vascular beds across organs with clear evidence of endothelial cell infection, inflammation, and apoptosis (Figure 1).¹¹ Viral elements were found within endothelial cells, with an accumulation of inflammatory cells and prominent cell death, as indicated by caspase 3 expression, in both endothelial and inflammatory cells (Figure 1). Varga et al describe a 58-year-old patient with diabetes and arterial hypertension who developed multiple organ failure, gut ischemia, and cardiac failure. Postmortem analysis of tissues identified prominent endothelial dysfunction and lymphocytic infiltrates in the lung, heart, kidney, small intestine, and liver. COVID-19 patients also frequently present with thick and copious mucus secretions within the lung alveoli. The reason is unknown but has been speculated to be reminiscent of what is found in patients with cystic

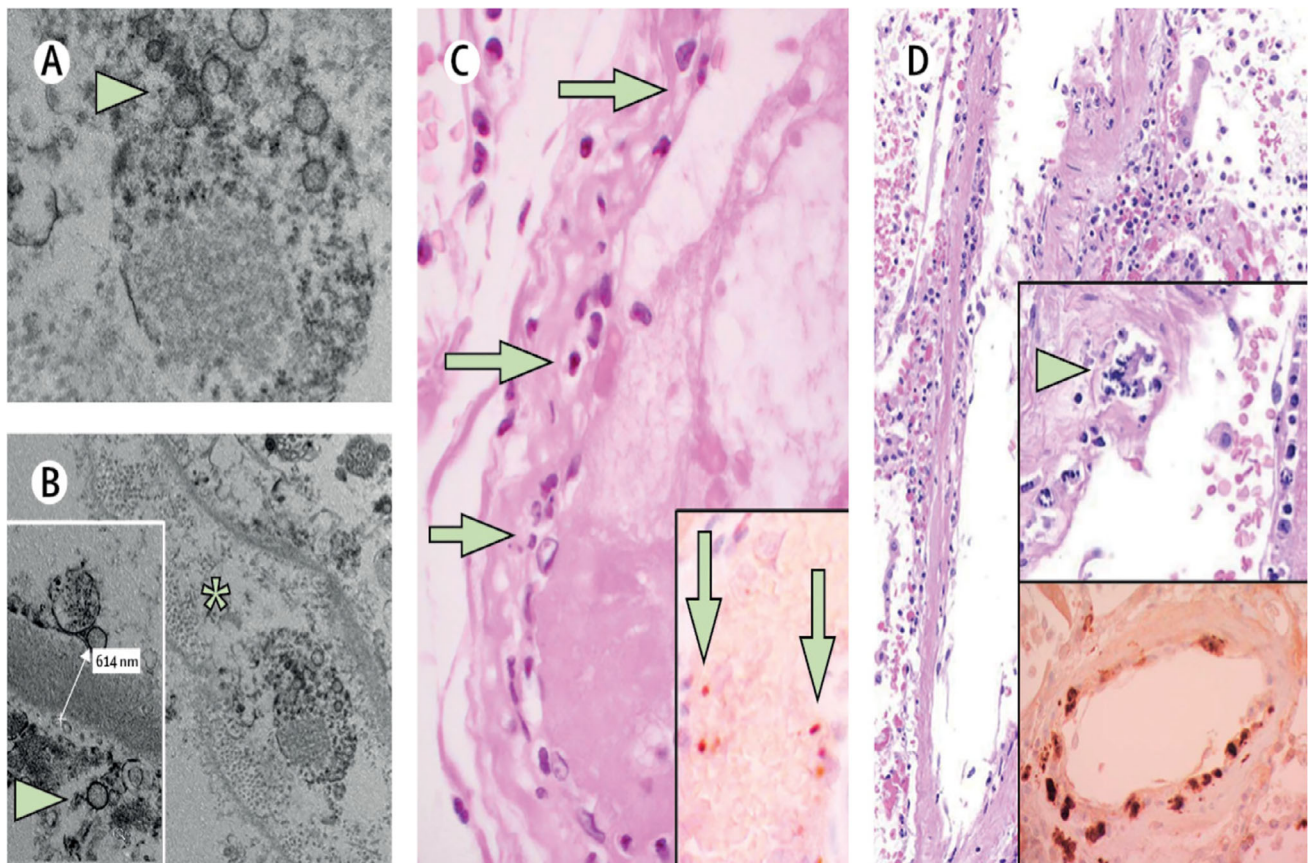


FIGURE 1 The Endotheliitis of COVID-19: (A, B) electron microscopy of kidney shows viral particles in endothelial cells of the glomerular capillary loops. B marks the peritubular space consistent with capillary-containing viral particles. (C) Small bowel resection specimen shows dominant mononuclear cell infiltrates within the intima along the lumen of many vessels. The inset of panel C shows staining of caspase 3, consistent with apoptosis of endothelial cells and mononuclear cells. (D) Lung specimen stained showed thickened lung septa, including vessel with mononuclear and neutrophilic infiltration; the lower inset shows an immunohistochemical staining of caspase 3 on the same lung specimen from correspondence in *Lancet* (Varga et al. April 17, 2020)¹¹

fibrosis and may be due to neutrophil activation and neutrophil extracellular trap formation.^{12, 13}

In another postmortem analysis study, Fox et al. reported findings from four patients with COVID-19.¹⁴ All were African American and had a history of obesity and medically treated hypertension. Three of the patients had insulin-dependent type II diabetes and two had known chronic kidney disease. In this study, gross examination of the lungs revealed edema with thick, white mucus and diffuse thrombi within the vessels (small and large). On histopathological analysis, a high degree of inflammatory cell infiltration, thickened capillaries, notable fibrin deposition, and CD61 megakaryocyte infiltration within small vessels and alveolar capillaries were found in all patients. These findings are consistent with classic ARDS, supporting the premise that patients with pre-existing compromise of cardiovascular function are prone to more severe disease and dying from COVID-19.¹⁵ This may in part also explain the predisposition of elderly patients to succumb to COVID-19 due to vascular compromise secondary to processes such as diabetes, atherosclerosis, and cardiac disease as they age. These findings have led to the speculation that COVID-19 may be a primary disease of the vascular endothelium, perhaps more specifically the aged or injured vascular endothelium (Figure 2).

3 | COAGULATION DEFECTS IN COVID-19 PATIENTS

In addition to the direct effects of viral infection on the endothelium in COVID-19 patients, it is possible that endothelial injury and inflammation may be a major driver of profound thromboses found in COVID-19 patients. Patients who are infected with COVID-19 develop coagulation patterns that are similar, but also distinct in many ways, to the disseminated intravascular coagulopathy pattern frequently associated with severe sepsis.^{15, 16} The COVID-19-related coagulopathy commonly manifests with a profound hyperthrombotic state, venous thrombotic events, high blood fibrinogen levels, high D-dimers (a sign of active fibrinolysis despite the high fibrinogen levels), consumption of anti-thrombin III (AT),¹⁶ and thrombocytopenia. High D-dimers and low AT¹⁷ are correlated with increased mortality, and many of these patients are currently being treated with therapeutic anticoagulation or tissue plasminogen activator (TPA) to prevent and lyse both micro- and macro-thrombi.¹⁸ However, the optimal timing and trigger for initiating anticoagulation and/or thrombolytic therapy remain highly variable between institutions largely due to a lack of clinical evidence on efficacy. Spiezia et al.¹⁵ recently

characterized the coagulation defects in COVID patients by thromboelastography (rotational thromboelastometry and thromboelastography [TEG]).^{15, 19} One can hypothesize that the significant systemic endothelial damage caused by the virus, compounded by unchecked inflammation, could fuel these thrombotic consequences.

More recently, Aid et al.²⁰ showed that rhesus macaques, similar to humans, infected with SARS-CoV-2 exhibited thrombosis, endothelial dysfunction, and endothelial disruption. Histopathologic examination of sections of lungs from both humans and rhesus macaques infected with SARS-CoV-2 demonstrated endothelial disruption and vascular thrombosis. Molecular pathway analysis of disease progression in macaques revealed upregulation of thrombosis, macrophages, platelet activation, and increase in pro-inflammatory markers. This study showcases how the interactions between inflammatory and thrombosis pathways lead to SARS-CoV-2-induced vascular disease. Taken together, these findings suggest that COVID-19 is a systemic disease and the endothelium is emerging as a critical platform in which a number of the clinically deleterious sequelae of the disease emerge. The endothelium can be designated as an organ that communicates systemically and, arguably, would be among the most important organs for controlling and maintaining systemic homeostasis.²¹⁻²⁴ It communicates throughout the organism and is the platform on which coagulation, inflammation, gas exchange, control of vascular integrity, and permeability take place in both health and disease. This widespread endothelial involvement of SARS-CoV-2 is likely a cause of the disease, particularly in those patients with severe systemic manifestations, and thus the endotheliopathy of COVID-19 (EOC) may represent a prime target for therapeutic interventions.²⁵

4 | THERAPEUTIC INTERVENTIONS TO TREAT THE ENDOTHELIOPATHY OF COVID-19

There is a valid rationale for utilization of therapies that stabilize, protect, and repair the vascular endothelium in COVID-19 patients. These strategies could potentially be used in combination with antiviral approaches and other targeted therapies that directly affect the virus to mitigate outcomes.²⁶⁻³⁰ There are a number of clinical studies being conducted to address the EOC, which is defined as being composed of coagulation disturbances, inflammation, and vascular instability as therapeutic targets. Studies modulating thromboses utilizing thrombolytic therapy such as TPA, enoxaparin, and heparin, for instance, are being run in trials currently.³¹ Anti-inflammatory therapies have also found a place in this

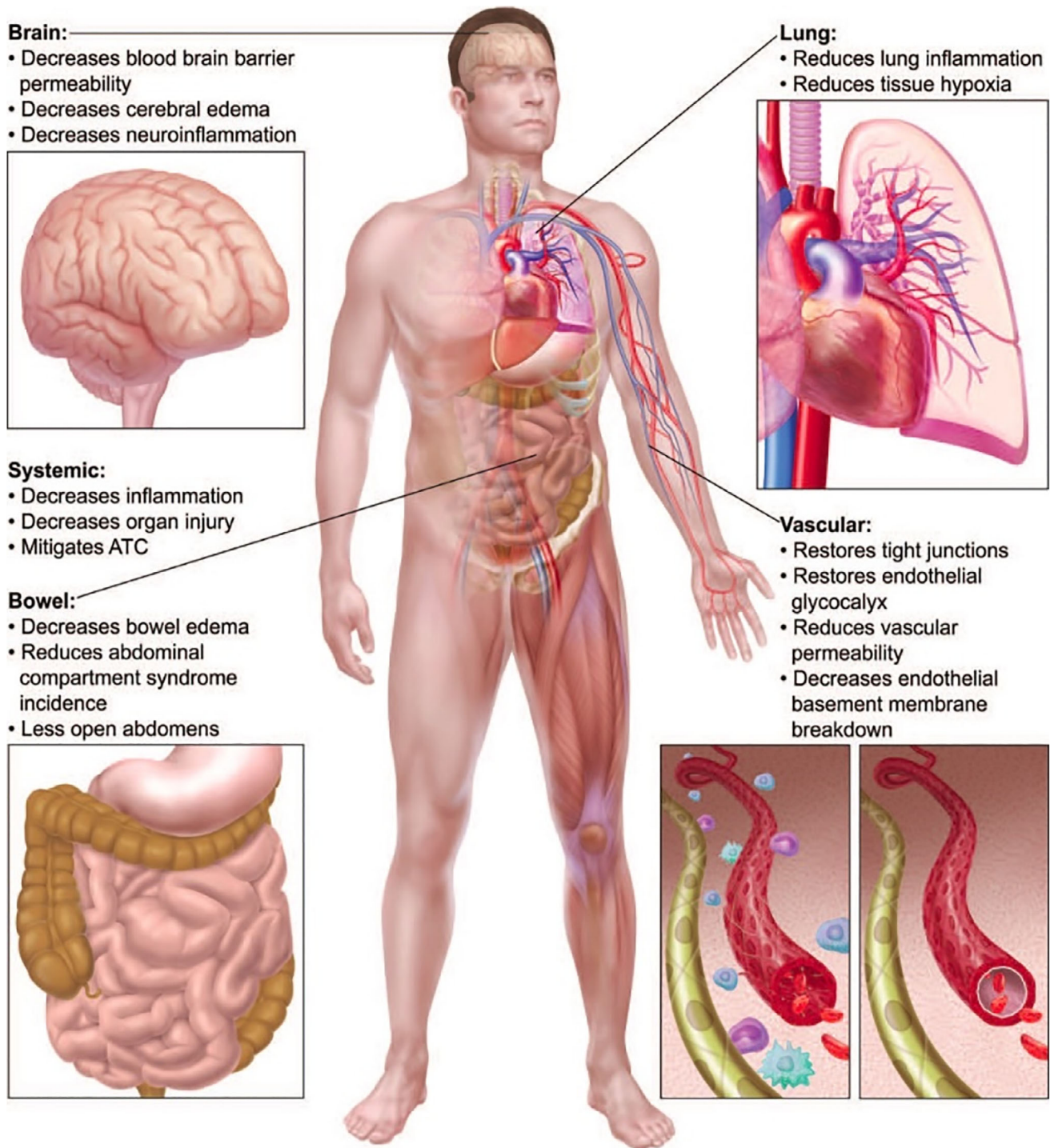


FIGURE 2 Plasma repairs the vascular endothelium damage to the endothelium by hemorrhagic shock, and crystalloid fluid resuscitation results in the endotheliopathy of trauma, which results in vascular leak, tissue edema, inflammation and end organ injury. This process is repaired by plasma- and platelet-based resuscitation⁸⁶

disease as is noted with the recent findings on corticosteroids recently reported by Horby et al. from England, which demonstrate approximately a 30% drop in mortality in critically ill, mechanically ventilated COVID-19 patients.³² The IL-6 antagonists that are currently in trials (NCT04363502) can also directly impact the endothelium

because IL-6 is produced by endothelial cells and is also highly activating to the endothelium; however, the results of these trials are still unknown. It is possible that addressing all or multiple parts of the EOC will be necessary to effectively treat the consequences of SARS-CoV-2. We have added some of these thoughts in this paper.

5 | COVID-19 CONVALESCENT PLASMA

Another approach that hypothetically can mitigate the EOC involves the utilization of COVID-19 convalescent plasma (CCP) for patients who are acutely ill. In the early stages of the pandemic, CCP was transfused into thousands of COVID-19 patients. The approach of using convalescent plasma has proven effective in the past for Ebola patients and was the rationale behind testing CCP in COVID patients.³³ However, more recently, in a placebo-controlled trial (NCT04383535), no significant clinical differences or mortality differences were found between patients who received 1 unit of CCP and those who received placebo (normal saline).³⁴ Limitations of this trial were that patients were already severely ill and hypoxic when they received the CCP and they only received 1 unit, which may not have been sufficient. It may be that earlier treatment with CCP over an extended period could prove beneficial. This has been more recently demonstrated in a paper published by Libster et al.,³⁵ where early administration of CCP in elderly patients who developed symptoms within 72 h were treated with high-titer CCP. Early administration of high-titer CCP against SARS-CoV-2 to mildly ill, infected seniors reduced COVID-19 progression. This finding, however, leaves many questions unanswered, such as what would the outcome be if it were compared to standard non-CCP fresh frozen plasma (FFP).

Another unanswered question is: what would be the result if the comparison group was low-titer CCP? Answers to these questions will aid in teasing apart the contributions of CCP versus FFP in treating SARS-CoV-2. However, what is clear is that the beneficial effect appears to be one that occurs with early administration of CCP and does not address the treatment of critically ill patients with high mortality rates. We hypothesize that early administration of CCP with neutralizing antibodies addresses the viral infection; however, once the EOC or pathophysiology of the disease has advanced, we hypothesize that these endpoints cannot be addressed by neutralizing antibodies to the virus. One can compare stopping the virus to stopping hemorrhage in trauma, which is the inciting event, but once the disease is advanced and secondary sequelae have begun, as they do in hemorrhagic shock patients, the damage has already begun to the vasculature and organs, and hence stopping hemorrhage alone is not enough to prevent the endotheliopathy of trauma (EOT).

The only way to truly know the contribution of the plasma from the anti-SARS-CoV-2 neutralizing antibodies is to isolate the neutralizing antibodies from the plasma and compare the isolated antibodies to standard plasma in preclinical or clinical studies. This would likely

not be a high-yield experiment especially since neutralizing antibody cocktails (i.e., from Regeneron and Eli Lilly) are indeed being developed and in use by Emergency Use Authorization for COVID-19. We do not doubt that the CCP antibodies may be of clinical benefit, but we do pose the question of whether the plasma part of CCP may be contributing as well to the noted beneficial effects. CCP is not the current standard of care in multiple hospitals and is rapidly being replaced by drugs such as IL-6 inhibitors and remdesivir.

Although CCP has not proven to be effective in treating advanced severe cases of COVID-19, what has emerged from trials with CCP is that plasma transfusion in these critically ill COVID-19 patients does not appear to be deleterious or harmful and to lead to increased thromboses, which has been a concern considering the hyperthrombotic state of COVID-19 patients. In a 5000-patient trial of those receiving CCP, increased thrombotic events were not found to be present in the CCP-treated group within the first 4 h of transfusion.³⁶ The goal of the trial was to assess the safety of CCP but not efficacy. The overall frequency of serious adverse events (SAEs) within 4 h following the transfusion of CCP was less than 1% and the 7-day mortality rate was 14.9%. The rate of SAEs definitely related to transfusion of CCP was objectively low ($n = 2$), hence supporting the safety of plasma transfusion in COVID-19 patients receiving 1–2 units.³⁶ These data support the safety of plasma transfusions in COVID-19 patients.

6 | THE RATIONALE FOR UTILIZING PLASMA TRANSFUSION TO TREAT THE ENDOTHELIOPATHY OF SARS-CoV-2 INFECTION IN COVID-19 PATIENTS: LESSONS LEARNED FROM TREATING BLEEDING TRAUMA PATIENTS

Distinctly different from CCP is standard donor plasma or FFP, which has the potential to be effective in COVID-19 patients based on its benefits in preclinical and clinical models of endothelial dysfunction, inflammation, and aberrant coagulation in trauma and hemorrhagic shock patients (Figure 2).³⁷ The clinical presentation of the endotheliopathy that occurs in severely injured trauma patients is reminiscent of COVID-19 patients. While CCP is currently limited due to the small available donor pool, standard plasma is immediately and widely available for the treatment of a pandemic level of patients.

It is of interest to note that in the early months of the pandemic, neutralizing antibody was not being assessed

in CCP, and thousands of patients actually received standard plasma without neutralizing antibodies. Fifteen to twenty percent of CCP units were negative for neutralizing or binding antibodies to SARS-CoV-2 (unpublished data, UCSF). This data is further supported in a paper published by Klein et al.,³⁸ where CCP from 126 patients was studied and 20% of them were found to not have neutralizing titers of antibodies. This study also revealed that being male, advanced age, and hospitalized resulted in increased neutralizing titers. This data suggests that a number of patients treated with CCP were actually receiving the equivalent of FFP, without any noted increase in complications. These studies do not demonstrate the efficacy of neutralizing antibody positive or negative plasma, which, based upon our knowledge of the benefits of FFP in trauma, may be due to the quantities administered and the timing during the course of the disease when they were administered. In trauma patients, hemorrhage accounts for the majority of preventable deaths in both military and civilian casualties.^{37, 39–41} In the acute care of bleeding trauma patients, goals for resuscitation and blood product transfusion have been defined by landmark retrospective and prospective studies in which whole blood or balanced ratios of red blood cells, plasma, and platelets improved survival and outcomes.^{37, 40, 42} Early administration of high ratios of FFP and platelets has also been shown to improve survival and reduce total blood component therapy requirements.^{37, 40, 42, 43} Plasma has the capacity to attenuate hemorrhage as well as mitigate many of the secondary vascular and inflammatory consequences of hemorrhage by decreasing MOF and subsequent death.^{44, 45, 46–49} Multiple observational studies suggest a decrease in ARDS, acute kidney injury (AKI), and MOF with increased use of plasma versus crystalloid as a primary resuscitation fluid.^{40, 50, 51}

Currently there are numerous clinical trials under way comparing the feasibility, safety, and efficacy of CCP versus FFP in early- and late-stage COVID-19 patients (NCT04589949, NCT04442191, NCT04392414, NCT04359810, NCT04421404, NCT04391101). FFP is the control arm for CCP. These trials, most of which are Phase II randomized trials, will provide further important information on the potential therapeutic benefits of standard donor FFP in COVID-19.

7 | PLASMA AND THE ENDOTHELIOPATHY OF TRAUMA

Traditionally, the therapeutic transfusion of plasma has been to correct coagulation, replace blood lost, and achieve hemostasis in bleeding patients by replacing

consumed, depleted, or diluted coagulation proteins. However, other potent non-hemostatic effects on the endothelium and inflammation have been described. Endothelial cells are one of the first cell types to come into contact with transfused plasma. FFP transfusion has been shown to attenuate vascular endothelial permeability and inflammation both in *in vitro* and *in vivo* mouse models of hemorrhagic shock (HS) and injury.^{52–58} Plasma-based resuscitation has been shown to decrease tissue edema and end-organ injury.^{55, 57–60} In rodent models of EOT, plasma has been shown to mitigate ARDS and AKI.⁵⁷ In swine, plasma resuscitation has been shown to decrease blood–brain barrier permeability, cerebral edema, and neuro-inflammation after severe hemorrhage and traumatic brain injury.^{44, 45, 61, 62} The triad of endothelial instability, immune dysfunction, and aberrant coagulation is known as the endotheliopathy of trauma or EOT, and they are all targets of plasma-based resuscitation.^{37, 59, 63, 64} Mechanistically, plasma has been proven to repair the endothelial glycocalyx, which serves as an effective barrier to leukocyte–endothelial and platelet–endothelial cell adhesion, by providing steric hindrance between receptor and ligand.^{65–67} The presence of SARS-CoV-2 viral elements within endothelial cells may cause disruption of the endothelial glycocalyx, which can lead to vascular compromise. Outside of clotting factors, hundreds of proteins have been identified in plasma, many of which have important biological functions and may be possible mediators of plasma's mitigation of EOT and preservation of the endothelial glycocalyx. Plasma-derived products such as prothrombin complex concentrate have been shown to inhibit vascular permeability *in vivo* in a mouse model of HS and injury.⁶⁸ Cryoprecipitate, which is also prepared from plasma and contains high levels of fibrinogen, is commonly administered in patients with hemorrhagic shock and trauma, and may also have endothelial protective effects similar to FFP.⁶⁵ The precise proteins in plasma and plasma-derived products that are responsible for mitigating endotheliopathy remain uncertain and warrant further investigation.

Concern over transfusion-related acute lung injury (TRALI) and other transfusion-related complications is often discussed in utilizing increased amounts of plasma; however, most authorities now describe its occurrence in less than 1 in 40,000 transfusions.⁶⁹ Evaluating the risk versus benefit is important when confronted with a lack of clear therapeutic interventions during this pandemic. The beneficial effects of plasma may be due in part due to its direct effects on the endothelium and also to its normalizing effects on inflammatory processes (both cellular and humoral) that induce blood–organ barrier permeability, tissue edema, and thrombosis.

8 | ADDRESSING CONCERNS OF TREATING HYPERCOAGULABLE COVID-19 PATIENTS WITH PLASMA

Given the thromboembolic complications observed in COVID-19 patients, reservations concerning the therapeutic use of plasma, classically considered to be a pro-coagulant, are understandable. However, research on trauma and hemorrhagic shock has challenged our understanding of the way in which plasma supports coagulation in patients with acquired coagulopathies. Plasma contains a balanced mixed of both pro- and anti-coagulant factors, and thus may represent an ideal solution for restoring homeostasis rather than being considered a purely pro-coagulant agent. Severely ill COVID patients have been reported to suffer from shock with an incidence as high as 67%.⁷⁰ Some of these patients may be hypocoagulable; however, most of them are hypercoagulable by TEG analysis. TEG parameters in COVID-19 patients typically show decreased K values as well as increased alpha angle and maximal amplitude.^{19, 71} Platelet counts are typically normal or increased, prothrombin time and activated partial thromboplastin time have been found to be close to normal, fibrinogen is increased, and D-dimers are dramatically increased. COVID-19 patients exhibit pathologic thrombosis resulting in tissue ischemia or infarction and organ failure. Acutely bleeding trauma patients also have periods of hypercoagulability, and hence the coagulopathy of COVID and the coagulopathy of severe hemorrhage present with patients that cycle between periods of being hyper and hypocoagulable.⁷² In trauma, plasma normalizes coagulation. In terms of sepsis, there is preclinical data suggesting benefits of plasma in organ failure^{73, 74} and there are currently trials being run testing plasma as a resuscitation fluid in sepsis. Similar to COVID-19 patients, patients with severe injuries and hemorrhage present with pronounced hypercoagulability initially with systemic, uninhibited thrombin generation,^{75, 76} which is associated with a later risk of thromboembolic complications.⁷⁷ Through animal models of trauma and HS, which recapitulate this hypercoagulable phenotype, we have learned that resuscitation with plasma normalizes this aberrant activation of the coagulation system by reducing thrombin generation in an AT-dependent manner. In vitro models in human trauma patient plasma reiterate these findings^{78, 79} and have further shown that in patients with profound hypercoagulability, plasma treatment reduces thrombin generation, whereas in hypocoagulable patients, plasma enhances thrombin generation.⁷⁸ Taken together, these findings demonstrate that plasma is neither specifically

pro- nor anti-coagulant. It provides balance to an otherwise imbalanced hemostatic system. In short, it is the ideal fluid to restore coagulation homeostasis.

9 | PLASMA IN NON-BLEEDING PATIENTS

Secondary to the findings on plasma's beneficial effects in trauma, there is equipoise to consider its use in other medical conditions such as sepsis that are also characterized by damage to the endothelial glycocalyx and vascular permeability. Fluid resuscitation is one of the mainstays in the acute management of sepsis; however, the optimal fluid to use is unclear. Chang et al. conducted a rat sepsis study^{74, 80} in which FFP significantly increased 48-h survival, improved the post-resuscitation PO₂ to FiO₂ ratio, and reduced the pulmonary edema. Compared to crystalloid fluids, plasma resuscitation increased 48-h survival, attenuated markers for inflammation, decreased endothelial injury, and decreased catecholamines. Crystalloid fluids have been shown to be hyperinflammatory and detrimental in critically ill patients.³⁷ An ongoing single-center, randomized clinical trial (NCT04580563) is addressing whether plasma is superior to crystalloid resuscitation in sepsis, albeit in non-COVID patients.⁸⁰⁻⁸²

10 | CASE STUDIES DEMONSTRATING THE FEASIBILITY OF TRANSFUSING PLASMA IN COVID-19 PATIENTS

These two cases are presented purely for the sake of proof of concept, to demonstrate the feasibility of administering plasma in severely ill COVID patients. Although there are risks associated with plasma transfusion (i.e., contamination, TRALI, TACO-transfusion-related cardiac overload), our team and the IRB at Elmhurst felt that the benefits outweighed the risks early in the pandemic when few other treatment options were available. It is also important to note that these cases are not a call for the immediate initiation of a clinical trial of standard plasma in COVID-19. We believe that further preclinical data is warranted in rodent and possibly primate models of COVID-19 to better study the mechanism of action and gain insight into the safety and efficacy of plasma in COVID-19.

In these cases, the plasma transfusion was specifically administered as an adjunct to standard of care over a period of 12 h. The reason for the infusion over 12 h was secondary to a concern of volume overload in patients who could develop compromised renal function. The

12-h infusion was approved by the hospital IRB so as to not put the two patients at risk. Although there is a large body of translational and clinical research demonstrating the numerous benefits of plasma transfusion, there are multiple questions remaining regarding the optimal timing, dosing, and duration of therapy in bleeding patients. We present here two representative case examples of COVID-19 patients who were treated with normal donor plasma (FFP) along with other routine intensive care unit (ICU) supportive therapies.

Patients were selected based on the presence of ARDS without evidence of any other organ failure. These two cases were reviewed and received a waiver from the Elmhurst Hospital Center IRB. The waiver was based on the premise that FFP has indeed been tested in non-bleeding, critically ill coagulopathic patients and shown endothelial and inflammatory benefits.⁸³ It is these previously published findings on FFP in bleeding and non-bleeding patients in shock that spurred the attending physicians, who were familiar with the data on FFP use in trauma, to utilize FFP to treat EOC.

10.1 | Case 1

A 72-year-old female with a history of hypothyroidism, hypertension, and depression residing at a nursing home was sent to the emergency room after a ground-level fall. Although no significant traumatic injuries were noted, the patient was found to be hyponatremic (sodium of 124) and was admitted to the medicine service. A test for SARS-CoV-2 infection was sent on admission and was positive. The patient developed hypoxia on hospital day 3 and was managed with noninvasive supplemental oxygen therapy until developing acute respiratory failure on hospital day 10. Chest X-rays obtained both immediately following intubation and in subsequent days showed diffuse bilateral infiltrates consistent with ARDS. The patient was intubated and transferred to the ICU. The patient had no available next of kin, therefore two physician consents were obtained, and she was treated with a 12-h course of 50 cc/h of FFP on ICU day 1. D-dimer values, both prior to and following intubation, remained around 400–500. Throughout her hospital course, PT/INR (prothrombin time/international normalized ratio) and PTT (partial thromboplastin time) remained normal. In the days following intubation, the patient required minimal ventilator settings (40% FiO₂ with a PEEP of 8; P/F ratios of >200) but required sedation and frequent suctioning of secretions to maintain O₂ saturations above 88. Her creatinine did not rise, no arrhythmias were noted, and her ventilator settings did not escalate over the following 2 days. She was extubated

on ICU day 3 without complication. The patient did not develop renal or other organ failure, and no evidence of thrombotic or deleterious consequences of the plasma transfusion were found.

10.2 | Case 2

A 75-year-old male with a history of mild asthma (prescribed an as-needed albuterol inhaler) and a distant history of colorectal cancer in the 1970s was admitted from the emergency room to the medicine service for shortness of breath and presumed COVID-19 (later confirmed). The patient was managed with noninvasive supplemental oxygen therapy for 1 week until developing acute respiratory failure on hospital day 8, at which point he was intubated and transferred to the ICU. Chest X-rays obtained both immediately following intubation and in subsequent days showed diffuse bilateral infiltrates consistent with ARDS. On ICU day 1, after obtaining telephone consent, the patient was treated with a 12-h course of 50 cc/h of FFP. At the time of his transfer to the ICU, D-dimers was trending downward from a maximum of over 40,000 on hospital admission to approximately 5300 just prior to intubation and to 3800 the morning after intubation. Following FFP administration, PT/INR and PTT remained normal, and the patient's D-dimer levels continued to decline over several days to approximately 500. On ICU day 4, his sputum cultures grew enterococcus, for which he was treated with cefepime. At ICU/ventilator day 13, the patient remained intubated, on moderate ventilatory settings (60% FiO₂ with a PEEP of 8; P/F ratios of 100–200). The patient demonstrated no sign of renal injury, arrhythmias, or end-organ damage. He showed no evidence of thrombotic or deleterious consequences of the plasma transfusion.

To reiterate the goal of including and briefly describing the two case reports was as proof of concept for feasibility of administering FFP to COVID-19 patients. Our hypothesis that FFP could be beneficial therapeutically was based on our knowledge of its efficacy in trauma in mitigating the EOT. Essentially, this was repurposing of a “drug,” as many of the therapies that have been tested for COVID-19 were at the early stages of the pandemic. At that time, in the height of the pandemic at Elmhurst hospital, there were 160 intubated patients in the ICU. The mortality for these intubated patients was approximately 95% and the availability of alternative therapies aside from hydroxychloroquine was limited and was the only alternative treatment being used with limited success as reported by the physicians attending to these patients. This is why the IRB granted permission to transfuse FFP into these two patients, based on the

premise that FFP had been shown to mitigate multiple endpoints that were similar in trauma patients and COVID-19 patients—specifically inflammation, coagulation, and vascular dysfunction. So in these two patients, an FDA-approved product (FFP) was administered, in an attempt to improve the EOC and outcomes in those two patients who had a 95% chance of dying in that ICU. As mentioned above, efficacy and safety cannot be assessed in these two cases. IND-enabling preclinical work could help support a much larger clinical to truly understand the therapeutic potential of FFP in COVID-19.

11 | IS CCP THE SAME AS FFP, ASIDE FROM THE PRESENCE OF ANTI-SARS-CoV-2 ANTIBODIES?

One point that is worthy of further investigation, from a transfusion standpoint, is whether CCP is the same at the proteomic and molecular level as FFP, aside from the presence of SARS-CoV-2 neutralizing antibodies. We hypothesize that CCP is distinctly different in its proteomic makeup from FFP. There are likely multiple plasma protein differences that have yet to be characterized. In our past studies, in preclinical models of hemorrhagic shock and trauma, it became clear that the beneficial effects of plasma in shock are due to the presence of a number of circulating proteins and peptides that are not clotting factors or related to the clotting cascade.^{63, 84} Whether these vasculo-protective proteins exist in the same concentrations in CCP is still unknown and warrants further investigation. Generally speaking, in sick individuals, plasma from sick patients such as patients who are in shock contain inflammatory factors for months after the initial insult.⁸⁵ It will be interesting, from the perspective of donor plasma, to study whether patients who have had COVID-19 are suitable donors. Proof of this being a potential concern is evident from a condition known as persistent inflammation, immunosuppression, and catabolism syndrome.⁸⁵ The plasma from previously critically ill patients was shown to contain harmful mediators due to a low-grade, chronic inflammatory state that persists for years.⁸⁵ It is possible that this plasma is not suitable for transfusion and has been associated with infections in sepsis. This has yet to be elucidated in COVID patients and, considering that there are indeed reports of a “cytokine storm” and long-term consequences of the disease (i.e., COVID-19 long haulers), the ex-COVID-19 patients’ “normal” plasma could potentially be unsuitable for transfusion months or even years later. Further investigation is warranted, and multiple groups are indeed working in this area.

12 | CONCLUSION

Early study of the pathologic effects of the SARS-CoV-2 virus reveal profound hypercoagulability and an endotheliopathy resulting in secondary organ failure likely due to microthrombi and endothelial dysfunction. CCP trials have demonstrated some efficacy when transfused early in the disease process; however, CCP has not proven beneficial in improving clinical outcomes in severely ill COVID-19 patients. What is clear from the studies with CCP, albeit with limited transfusion of an average of 1 to 2 units, is that there was no deleterious effect of plasma treatment such as increased thrombotic events, which was a primary concern. Logistically, normal donor plasma is readily available in significant supply. Logistics could be enhanced by some of the newer dried plasma products and plasma-derived products that are currently under development. Based on our understanding of plasma-based resuscitation in trauma, we hypothesize that transfusion of plasma to at-risk COVID-19 patients, over extended periods of time (days), could be clinically beneficial in preventing the EOC and the secondary consequences of EOC, which include organ failure. Strengthening our paper in terms of the feasibility of transfusing FFP in critically ill patients is the presentation of two case reports from Elmhurst hospital in New York. This hospital treated high numbers of COVID-19 patients in April 2020 with resulting high mortality. These two patients were administered FFP for 12 h (not CCP), and the data suggest that FFP transfusion was feasible. These two patients were transfused during the early stages of the pandemic, and the death rate at that time in intubated ICU patients was as high as 95%, with the majority of the patients exhibiting systemic end-organ failure. The numerous prospective, randomized, controlled trials that are under way comparing CCP to FFP in COVID-19 patients will provide important information on FFP transfusion. This paper advocates for further preclinical work to elucidate the mechanisms of action followed by clinical investigation into the use of normal donor plasma (FFP) to treat COVID-19 patients and mitigate EOC.

CONFLICT OF INTEREST

SPati has a contract for a research project with CSL Behring Inc. JBH is a co-founder and on the Board of Directors of Decisio Health, on the Board of Directors of QinFlow and Zibrio, a Co-inventor of the Junctional Emergency Tourniquet Tool, and an adviser to Arsenal Medical, Cellphire, Spectrum, and PotentiaMetrics. MAS is a consultant to Velico Medical Inc. Dr. Martin has none to report. JCC has funding from and is an adviser to Grifols. RK has none to report. AC is an active duty

officer in the US Army and has no conflicts of interest to declare. EF has none to report. RS has none to report. CW is a co-founder of Decisio Health and receives funding through his institution from Grifols. AT and MB have disclosed no conflicts of interest.

AUTHOR CONTRIBUTIONS

Shibani Pati: Contributed to the intellectual thoughts; writing of the manuscript. **Erin Fennern:** Contributed to the intellectual thoughts; writing of the manuscript; involved in collecting; presenting the data for the two case reports. **John B. Holcomb:** Contributed to the intellectual thoughts; writing of the manuscript. **Mark Barry:** Contributed to the intellectual thoughts; writing of the manuscript. **Alpa Trivedi:** Contributed to the intellectual thoughts; writing of the manuscript. **Andrew P. Cap:** Contributed to the intellectual thoughts; writing of the manuscript. **Matthew J. Martin:** Contributed to the intellectual thoughts; writing of the manuscript. **Charles Wade:** Contributed to the intellectual thoughts; writing of the manuscript. **Rosemary Kozar:** Contributed to the intellectual thoughts; writing of the manuscript. **Jessica C. Cardenas:** Contributed to the intellectual thoughts; writing of the manuscript. **Renee Spiegel:** Contributed to the intellectual thoughts; writing of the manuscript; involved in collecting; presenting the data for the two case reports. **Joseph F. Rappold:** Contributed to the intellectual thoughts; writing of the manuscript. **Martin A. Schreiber:** Contributed to the intellectual thoughts; writing of the manuscript.

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