



HOW DO I?**How do I implement an outpatient program for the administration of convalescent plasma for COVID-19?**

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Abbreviations: BPA, Best Practices Alert; C3PO, Convalescent Plasma in Outpatients With COVID-19; CCP, COVID-19 convalescent plasma; CSSC, Convalescent Plasma to Limit SARS-CoV-2 Associated Complications study; COVID-19, Coronavirus Disease-2019; EUA, emergency use authorization; FDA, United States Food and Drug Administration; HICs, high-income countries; IV, intravenous; LMICs, low- and middle-income countries; mAb, Monoclonal antibody; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Abstract

Convalescent plasma, collected from donors who have recovered from a pathogen of interest, has been used to treat infectious diseases, particularly in times of outbreak, when alternative therapies were unavailable. The COVID-19 pandemic revived interest in the use of convalescent plasma. Large observational studies and clinical trials that were executed during the pandemic provided insight into how to use convalescent plasma, whereby high levels of antibodies against the pathogen of interest and administration early within the time course of the disease are critical for optimal therapeutic effect. Several studies have shown outpatient administration of COVID-19 convalescent plasma (CCP) to be both safe and effective, preventing clinical progression in patients when administered within the first week of COVID-19. The United States Food and Drug Administration expanded its emergency use authorization (EUA) to allow for the administration of CCP in an outpatient setting in December 2021, at least for immunocompromised patients or those on immunosuppressive therapy. Outpatient transfusion of CCP and infusion of monoclonal antibody therapies for a highly transmissible infectious disease introduces nuanced challenges related to infection prevention. Drawing on our experiences with the clinical and research use of CCP, we describe the logistical considerations and workflow spanning procurement of qualified products, infrastructure, staffing, transfusion, and associated management of adverse events. The purpose of this description is to facilitate the efforts of others intent on establishing outpatient transfusion programs for CCP and other antibody-based therapies.

KEYWORDS

ambulatory care, antibodies, blood transfusion, COVID-19, COVID-19 serotherapy, monoclonal, plasma

1 | INTRODUCTION

Since the initial description of SARS-CoV-2 in China, the rapid spread of this virus has led to a pandemic of historic importance. Treatment options at the start of the COVID-19 pandemic were understandably few, prompting the revival of a venerable approach, passive immunotherapy through the transfusion of convalescent plasma. Transfusion of convalescent plasma (i.e. plasma that has

been harvested from donors who have recovered from a disease of interest) has been used for over a century to treat numerous infectious diseases.¹ Data pertaining to the efficacy and safety of convalescent plasma were generally favorable but limited to observational reporting. Prior to the COVID-19 pandemic, clinical trials of convalescent plasma were uncommon, yielding mixed findings due to the heterogeneity of study design, patient population, infecting pathogen, the timing of administration

relative to disease time course, dose, and the controls used in previous studies.²⁻⁴

Given the authors' experience executing two multisite outpatient transfusion trials,^{5,6} we share our expertise in establishing a multisite framework regarding treatment logistics, with a goal of facilitating the efforts of others who may wish to implement outpatient programs for the transfusion of COVID-19 convalescent plasma (CCP).

1.1 | Experience with outpatient COVID-19 convalescent plasma and rationale for its use

Studies of CCP have been overwhelmingly skewed toward hospitalized patients with severe diseases. Since the severe disease is caused by an over-exuberant inflammatory response and CCP functions primarily as an antiviral, it is not surprising that studies in patients with severe disease have been inconsistent in demonstrating efficacy. In fact, the summary findings are consistent with knowledge prior to the pandemic: administration of CCP in moderate to severe COVID-19 late in the disease course has limited—if any—clinical utility,⁷ which likely forged the basis of a recommendation by the World Health Organization against the use of CCP for COVID-19. Similar observations apply to the use of mAb therapies, which were shown to be effective in preventing the progression of disease in outpatients but had little or no efficacy in hospitalized patients.⁸

In contrast, the administration of high titer CCP early after symptom onset has been shown to be both safe and effective, conferring a lower risk of hospitalization and death compared to controls.⁹⁻¹¹ Implementation of outpatient clinics relieves the burden on emergency departments, particularly during periods of increased activity. However, studies of CCP in outpatient subjects, a population that better approximates early or mild disease, are comparatively rare. One clinical trial showed significantly lower rates of progression of respiratory disease in elderly patients who received CCP.¹² Another study, the Convalescent Plasma in Outpatients With COVID-19 (C3PO) clinical trial focused on patients with COVID-19 seeking care in an emergency department.¹³ Although administration of CCP did not prevent hospitalization in this trial, the high number of participants who were admitted during the index visit suggests that the trial may have selected patients with more advanced diseases, likely influencing the results.¹³ In the largest outpatient trial of CCP to date, the Convalescent Plasma to Limit SARS-CoV-2 Associated Complications study (CSSC-004), early administration of CCP (i.e., within 9 days of symptom onset) to outpatients was shown to be safe and was associated with a 54% relative risk reduction in hospitalization, which increased to 80% if given within five days of symptom

onset.⁵ These collective findings have informed clinical guidelines supporting the early use of CCP.¹⁴ In late December 2021, the US Food and Drug Administration (FDA) amended their emergency use authorization thus allowing for CCP use in both the outpatient and inpatient settings, albeit in immunocompromised patients.¹⁵ CCP is also an option for hospitalized patients who do not qualify for other available antiviral therapies due to safety concerns or contraindications, such as pregnant women, individuals with advanced chronic kidney disease, or decompensated liver cirrhosis.

2 | APPROACH (TABLE 1 AND FIGURE 1)

Establishing an outpatient transfusion program for CCP requires several key elements, which we list below. Although the focus is on CCP, the same infrastructure and workflow could be adapted for the infusion of other parenteral preventive and treatment agents (Table 1 and Figure 1).

2.1 | Procurement of donor CCP with adequate antibody levels

As CCP is an investigational blood product, its production and use must conform to specifications outlined by the regulatory bodies of the country in which it is being administered. In the US, this falls under the purview of the US FDA, which stipulates that blood products may only be collected by registered and licensed blood collection facilities. The regulatory body is also responsible for establishing donor eligibility requirements, which have been adjusted as new data have emerged throughout the pandemic. Early in the pandemic, a variety of approaches (e.g., mining testing databases with automated referrals, conventional and social media, etc.) were employed to direct recently recovered donors to blood centers.¹⁶ The collection is typically undertaken using apheresis technology, at least in high-income countries, given its higher yield of plasma units per donation (up to 3–4 units for a large donor) compared to whole blood collection. Donors must be at least 10 days post-complete resolution of symptoms of COVID-19 prior to plasma collection.¹⁷

Testing for the presence of anti-SARS-CoV-2 antibodies, in addition to screening for blood-borne pathogens, ABO typing, and HLA antibody screening (in the case of parous women), is a prerequisite for qualification as CCP. Antibody thresholds for qualification of CCP have been continuously refined over the course of the pandemic. Formal neutralization assays are impractical

TABLE 1 Essential components of outpatient plasma infusion site

Essential factors	
Blood Bank	<ul style="list-style-type: none"> Established relationship with blood banking team with interest and understanding of participation in outpatient transfusion program Inventory management plan to assure adequate CCP supply of all ABO types
Staffing	<ul style="list-style-type: none"> Well-trained, flexible, personnel with experience in transfusion medicine Redundant staffing plan to allow for absences
Policies and documents	<ul style="list-style-type: none"> Organizational chart to support chain of command Well defined infection prevention requirements and strategy Consent documentation for use of investigational products that includes research use of data and/or samples if applicable Emergency preparedness plans; includes protocols for management of transfusion reactions and patient resuscitation Established policy pertaining to transfusion of out of Group plasma
Infrastructure	<ul style="list-style-type: none"> Adequate space and equipment to perform transfusions Appropriate infection control to reduce transmission Capacity to manage transfusion-associated adverse events, with availability of resuscitation medications, equipment and trained personnel Electronic medical record access
Communication	<ul style="list-style-type: none"> Clear communication plans between referring providers, patients and CCP scheduling team Devices to improve communication between patient infusion rooms and central staffing work center
Transportation	<ul style="list-style-type: none"> Transportation services for patients to get to and from the site when infectious Transportation for ABO typing to get from infusion center to blood bank laboratory and for plasma units to get to infusion center

for high throughput screening and remain difficult to standardize. Rather, a variety of assays have been validated for use whereby a defined antibody level has been shown to correlate with neutralization.¹⁷ CCP needs to meet the qualifying criteria of the FDA EUA prior to being considered eligible for transfusion.

2.2 | Distribution and inventory management

In general, institutional blood banks maintain the inventory of CCP. Ideally, there should be sufficient units of each ABO compatible type to meet clinical demand. The collection of certain blood types has proven to be challenging, notably Group AB (i.e., universal donor) given the low proportion of the population (~4%) who are Group AB; these donations are frequently earmarked to support the emergency use of plasma for the management of bleeding. Group AB plasma is scarce: in routine trauma resuscitation, Group A plasma may be substituted if allowable by institutional policy.¹⁸ Unlike plasma, which is used routinely for the management of bleeding and coagulopathy, the investigational status of CCP, imparts less flexibility regarding its use. Ideally, an institutional policy pertaining to out-of-group plasma would be devised prior to the implementation of transfusions. The risk and benefits should be discussed with the patient and an appropriate disclaimer should be included in the transfusion consent documents.

At the start of the pandemic, clinical demand for CCP exceeded availability. Following rapid scaling up of the collection, a standing inventory was achieved at most major blood centers. A standing inventory of CCP is important to handle surges in demand (e.g., due to emerging variants). Vaccination and a declining incidence of COVID-19 allied with evidence of futility in late-stage disease contributed to waning demand and collection ceased. Consequently, extant CCP inventories of CCP were poorly matched to later variants such as delta and omicron.¹⁹ This underscores the need to maintain a minimum inventory of CCP and ongoing capability to recruit new donors, particularly those who have recovered from infection with a virus that is similar to that which has infected the intended recipient. Temporal and geographic matching is ideal but is also logistically challenging. Despite imperfect matching, qualified CCP (per FDA definition) is still considered to be beneficial.

2.3 | Infrastructure

Administering clinical care during a pandemic to patients who are potentially infectious requires special infrastructure that is well suited for infection prevention to assure the safety of patients, staff, and visitors in health care facilities. The establishment of temporary facilities, as shown in Figure 2, is one example of a successful strategy. The facilities as depicted in Figure 2 were dual purpose, whereby they were used both for the treatment of COVID-19 (e.g., with monoclonal antibodies) as well as

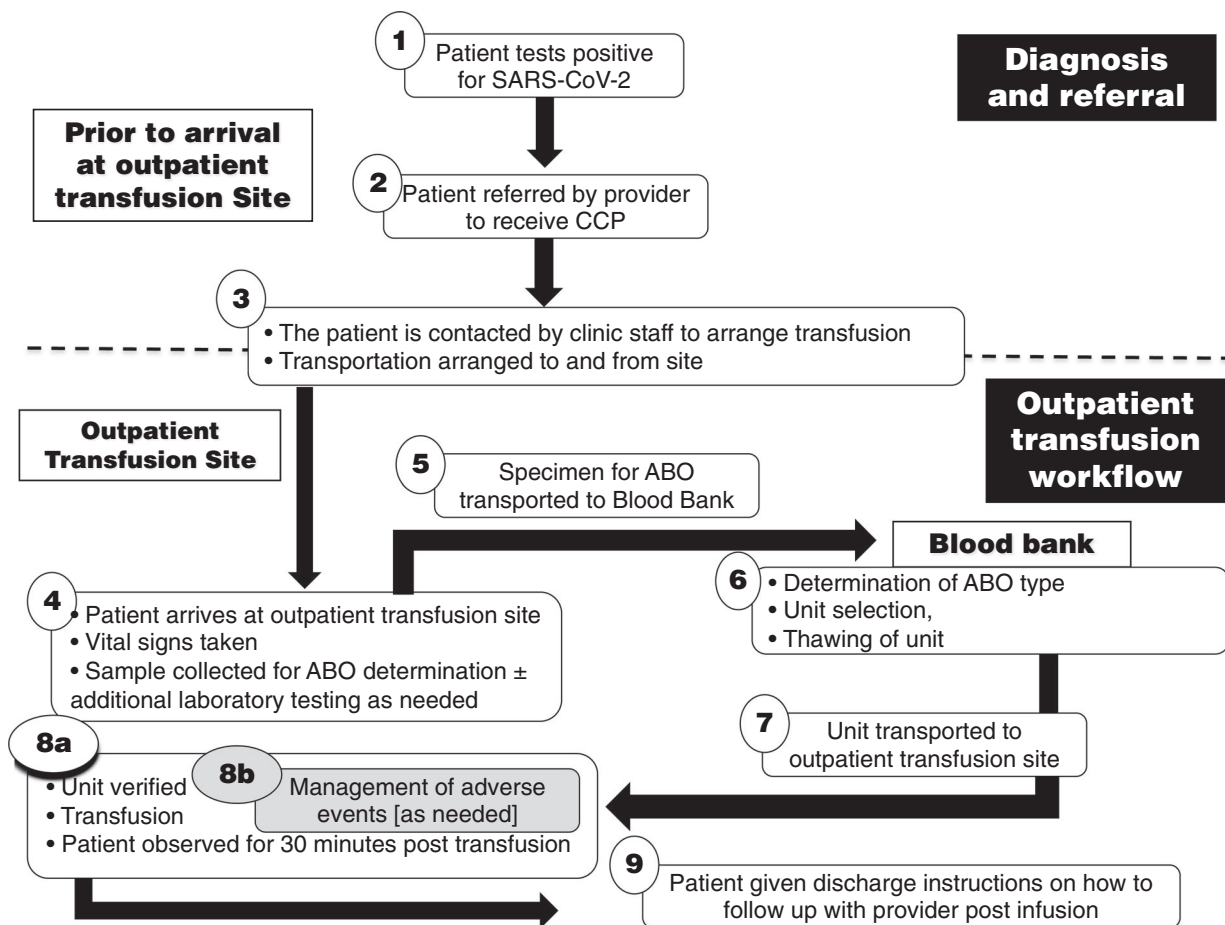


FIGURE 1 Workflow of outpatient transfusion of convalescent plasma

for the administration of CCP. Many outpatient transfusion and infusion centers administer immunosuppressive or chemotherapy to vulnerable populations and collocation with patients having active SARS-CoV-2 infection is a high risk for such groups. Within the CSSC-001 and CSSC-004 (i.e., a sister outpatient study to CSSC-001 to determine whether administration of CCP as post-exposure prophylaxis prevented infection),⁶ many of the sites used transfusion facilities that were outside of regular care locations, including annexes from emergency departments or transfusion sites or portable treatment facilities constructed with tents and trailers. This segregation of treatment sites from routine cares sites was a common infection prevention solution. This arrangement adds logistical complexity for patients and treatment products alike. One alternative approach to establishing a new outpatient CCP transfusion site is to repurpose pre-existing infrastructure for transfusion, such as negative pressure rooms that are designed for the care of patients with airborne infections (e.g., tuberculosis).

Construction of safe non-hospital clinical care sites requires facilities management to ensure reliable electricity, temperature control, appropriate airflow and ventilation,

and clinical engineering to ensure adequate supplies including IV poles and pumps equipment to assess vital signs and portable medication carts, and information technology (IT) to enable access to electronic medical record to facilitate orders and communication system either by cable or Wi-Fi. (Figure 2). Immediate access to certain rescue medications is necessary to treat infusion reactions, including antihistamines and glucocorticoids; those medications should be stored in the infusion center. Necessary equipment and medications must be inspected and kept up to date. Staff must clean each unit between patients and perform terminal cleaning at the end of each day. Comfortable personal protective equipment is needed for all staff members to ensure adherence to infection control standards. Communication devices between individual transfusion pods and a central area where staff may be working are necessary to allow patients or staff to alert others if they need help or have a question.

Separate disabled accessible restroom facilities must be clearly labeled for infected patients, persons under investigation, and medical staff. The treatment visit, including CCP infusion, typically lasts up to 2 h and

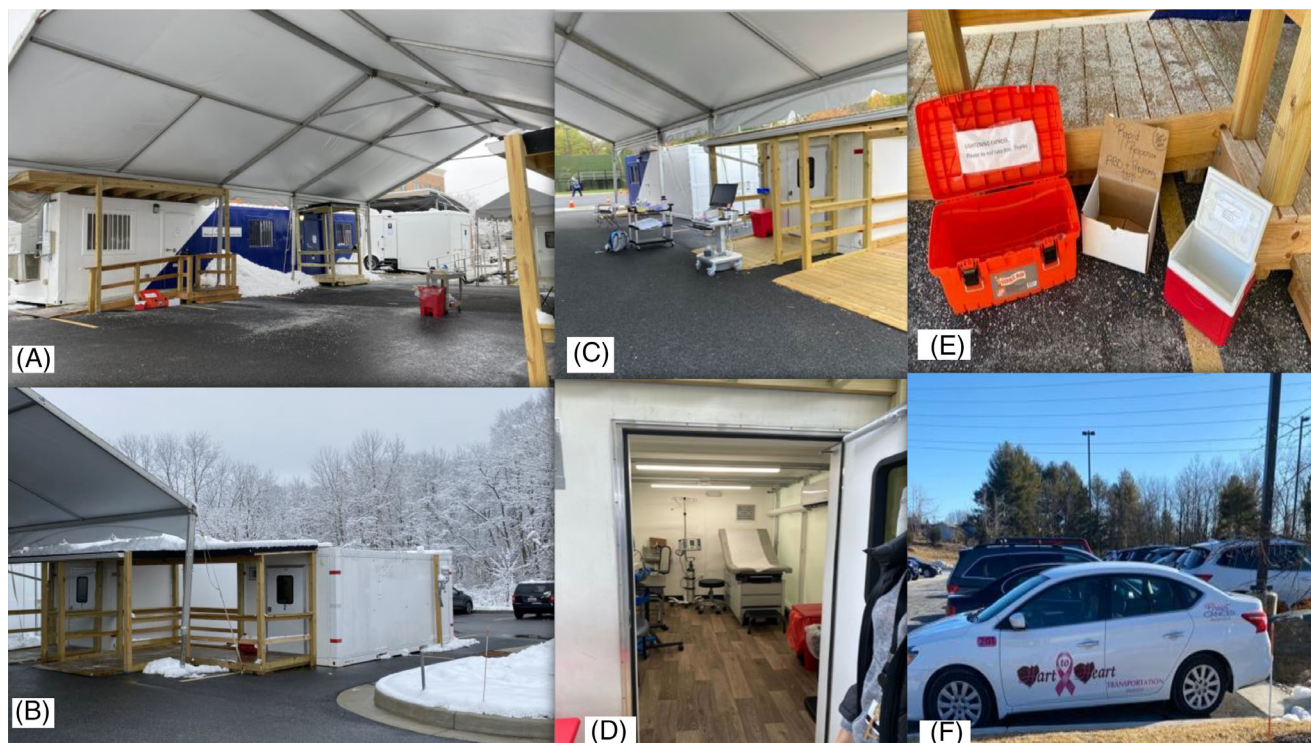


FIGURE 2 Photographs of an outpatient infusion site. (A) Pod for clinical staff workspace. (B) Exterior of patient infusion pods. (C) Donning and doffing stations and computer for entering vitals outside of patient infusion room. (D) Patient infusion room with chair and exam table, crash cart, oxygen, and equipment for infusion and assessment of vital signs. (E) Transportation coolers for samples to go to blood bank laboratory and coolers to be returned to blood bank after plasma infusion. (F) COVID-19 safe transportation for patients to and from infusion site [Color figure can be viewed at wileyonlinelibrary.com]

may extend to 4 h if ABO determination is performed during the same visit. The provision of snacks, beverages, blankets, and access to Wi-Fi improves patient satisfaction.

2.4 | Pre-transfusion recipient testing

Potential transfusion recipients require determination of ABO type prior to transfusion. For regulatory compliance, both a type and screen and a second sample for confirmation of ABO type are needed if a historical type is not on file. This may prove challenging to outpatient programs, as it adds time to an outpatient visit. One option is to collect two separate specimens (e.g., 5–10 min apart). An alternative approach is to use an electronic patient identification system.²⁰

Plasma transfusion is typically restricted to group-specific or ABO compatible units to mitigate the risk of hemolysis with the infusion. The rationale for this requirement has been debated given that ABO-incompatible platelet units, containing large volumes of plasma, are routinely transfused without adverse effects. Nonetheless, institutional guidelines for the administration of ABO-

incompatible plasma may differ, and CCP transfusion must adhere to local requirements.

Although the process of ABO typing is relatively rapid requiring only 10–60 min, it may be associated with additional logistical complexity when the blood bank is situated distant from the transfusing site. Options include on-site determination of the ABO type or the use of a dedicated courier service to shuttle products and specimens between the satellite recipient transfusion site and a centralized blood bank. While typing and transfusion should ideally be completed in a single encounter, next-day transfusion (i.e., typing on Day 1 and transfusion on Day 2) may be more feasible for patient comfort and patient time burden.

2.5 | Transportation

There are established standards pertaining to how blood products are transported, specifically regarding temperature monitoring. Ideally, plasma should be transfused within 24 h of thawing and stored at 1–6 degrees Celsius. Once thawed, CCP could be stored for up to 5 days as “Thawed Plasma” according to institutional policies given

that antibodies should remain stable due to their long half-lives.²¹ Compliance with the institutional policy is essential. Thawed plasma should be transported to the infusion site on ice in appropriately labeled validated transport containers (i.e., coolers or mobile refrigerators). This may require a dedicated courier between the outpatient transfusion site and the blood bank, if not contiguous.

2.6 | Staffing an infusion site

Operating a therapeutic antibody infusion site requires employees of different skill levels working in a coordinated fashion. The critical step to initiate the process is linking patients recently diagnosed with infection to treatment sites. Notifying patients and providers of available treatment options at the time of diagnosis of SARS-CoV-2 infection, and/or in follow-up electronic communication, is strongly recommended. An electronic medical record Best Practices Alert (BPA), sent to providers, was helpful in the timely referral of patients to CCP research sites. A scheduling team that is available beyond traditional working hours (including on weekends) is important, as referrals may be received throughout the day and scheduling of the patient requires transportation of the patient and the plasma to and from the infusion site. It is recommended that referral and transfusion orders are undertaken by separate individuals whereby the actual transfusion orders are prescribed by the staff physician at the outpatient transfusion site. If the transfusion site is entirely separate from the referring provider, testing needs to be repeated at the transfusing facility. This is particularly relevant to those patients who were diagnosed based on point of care tests by a referring provider.

At the transfusion site, required pre-transfusion activities include confirmation of patient identity and that the appropriate blood product has been received. Two providers (e.g., a transfusionist and a physician or advanced practice clinician) are required. Providers should receive the necessary training for specimen collection, starting intravenous (IV) lines, transfusion, and managing adverse events/transfusion reactions. For larger sites that are treating multiple patients simultaneously, adequate nursing/clinical staff is imperative. A physician or advanced practice clinician with clinical privileges should be available to respond to any suspected transfusion reactions or patients who arrive with severe COVID-19. The facility should have a well-developed emergency response plan: it is to be expected that some patients will arrive with or develop significant hypoxia or hypotension, chest pain or other COVID-19 related symptoms, thus requiring emergency stabilization. This may involve a response

from a hospital's critical response team or community emergency services. Ambulance access to the treatment facility must be considered in selecting a site for transfusion.

2.7 | Transfusion procedures and management of adverse events

Health care facilities have developed standardized protocols for documentation and infusion of outpatient regulated blood products which can safely be adapted for the infusion of CCP. Providers who are basic life support trained, should administer the infusion per institutional policy, and attend to the patient throughout the infusion and post-infusion observation period. Infusion rates are generally kept at 500 ml/h with vital signs taken immediately prior to infusion, 10–20 min after the start of the infusion, at the completion of the infusion, and at 30–60 min post-infusion. While transfusion of CCP is typically confined to single-unit transfusions, there may be scope for transfusion of multiple units for selected patient groups (notably immunosuppressed patients). That decision should be undertaken in concert with infectious diseases consultation.

Staff should be trained to recognize and manage any complications including allergic transfusion reactions.²² The latter comprises a spectrum spanning simple, uncomplicated urticarial reactions requiring antihistamines and prolonged observation, up to and including anaphylaxis requiring epinephrine. Providers need to pay attention to the recipient's ability to tolerate large volumes to mitigate the risk of transfusion-associated circulatory overload. Increasing the intervals between transfusions and/or administration of low dose diuretics may be considered in certain at-risk patients such as those with underlying cardiorespiratory disease. All staff should be familiar with the crash cart, and processes for escalating care, including how to care for a hypersensitivity reaction as well as any patient who develops progressive illness from their underlying COVID should be developed, reviewed, and practiced.

If an adverse event develops during infusion, the infusion may be slowed or stopped as per the judgment of the on-site clinician. Severe transfusion reactions that occur while the patient is still on-site, while uncommon, may require treatment and referral to the emergency department as needed. Following completion of the infusion, the patient should remain in the infusion area under observation for 30–60 min post-infusion. After that time, if the patient is not experiencing any adverse events, they may be discharged home.

A written post-infusion information sheet that lists the risks and possible complications of blood transfusion should be given to the patient prior to discharge. Depending upon the severity and nature of the complication, patients and/or their caregivers, should be advised to contact their healthcare provider or call emergency services.

2.8 | Lessons learned

Having administered over 1100 outpatient transfusions during the pandemic, many of which were performed at non-traditional infusion centers, we have learned to be prepared for the unexpected, including staffing shortages, rapidly changing clinical guidelines, and unexpected weather. Staffing shortages have been an enduring challenge throughout the health care system during the pandemic. A backup schedule for each position in the system (i.e., strategic redundancy) ensures continuity of care if any one individual is unexpectedly unable to work. It is essential for staff to be flexible, to have an emergency plan in place for unanticipated delays in care, and to develop communication strategies for notifying patients and the blood bank if a delay because this is a time-dependent intervention.

2.9 | CCP in low- and middle-income countries

Although a promising therapy for low-resource settings, there are important differences in practice in high-income countries (HICs) that must be considered.^{23,24} Acknowledging the heterogeneity beneath a broad characterization of LMICs, the infectious risk is higher in LMICs in large part due to suboptimal donor selection and laboratory screening.^{25,26} There are also differences in the collection. In HICs, CCP has been collected through apheresis. The latter is a highly efficient approach yielding 2–3 units of CCP per collection. However, apheresis is not widely available in many LMICs. Instead, plasma (including CCP) may be produced through the process of separation from whole blood. Separation is simple to perform and is able to be achieved at a significantly lower cost, given that there is no requirement for apheresis equipment and the associated technical expertise needed to perform the procedure. Another consideration is competing priorities. There is a massive unmet need for blood in LMICs.²⁷ This multifaceted problem could impact the necessary availability of appropriate and willing donors. Early in the pandemic, the possibility of sharing CCP with LMICs was raised²³;

however, due to the number of regulatory and logistical barriers, this was impractical. Thus, local sourcing of CCP is important.²⁸

3 | CONCLUSION

When administered early in the disease course, infusion of CCP with antibody levels against SARS-CoV-2 spike protein that are at or above the FDA qualification threshold can help prevent complications from COVID-19, including hospitalization and death. Setting up a plasma infusion center during a pandemic can be challenging. However, lessons learned from sites that have set up outpatient SARS-CoV-2 mAb infusion centers and/or overseen clinical trials that used CCP should facilitate future efforts. Assuring adequate staffing with appropriate training and experience, patient safety and comfort, communication between collecting and infusion teams as well as patients, and with appropriate flexibility among teams working together will optimize clinical outcomes.

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CONFLICT OF INTEREST

Evan M. Bloch reports personal fees and non-financial support from Terumo BCT, Grifols Diagnostic Solutions, and Abbott Laboratories, outside of the submitted work; Evan M. Bloch is a member of the United States Food and Drug Administration (FDA) Blood Products Advisory Committee. Any views or opinions that are expressed in this manuscript are those of the author's, based on his own scientific expertise and professional judgment; they do not necessarily represent the views of either the Blood Products Advisory Committee or the formal position of the FDA, and do not bind or otherwise obligate or commit either Advisory Committee or the Agency to the views expressed.

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