DEPARTMENT OF HEALTH & HUMAN SERVICES

FOOD AND DRUG
ADMINISTRATION
Silver Spring, MD 20993

CLINICAL REVIEW MEMO

Re:	**BLA 125396/21**
Product	COVID-19 Convalescent Plasma
Sponsor	Stanford Blood Center
Reviewed	Carlos Villa MD, PhD, Associate Director for Special Programs
Date Reviewed	9/15/2025
To	File
Through	Wendy Paul MD Deputy Director Division of Blood Components and Devices
ADD	4/3/2026

Executive Summary

Scientific evidence from adequate and well-controlled trials of COVID-19 convalescent plasma supports that it is safe and effective in the treatment of COVID-19 when sufficiently high titers are used in patients with immunosuppressive disease or receiving immunosuppressive treatments. The risks of CCP are comparable to conventional plasma, and rates and types of transfusion reactions are similar. The sponsor's approach to donor eligibility and product qualification results in CCP with high titers. In treatment of patients with COVID-19 and immunosuppressive disease or receiving immunosuppressive treatments, the benefits of CCP are likely to outweigh the risks. I recommend approval of BLA 125396/21 for licensure of COVID-19 Convalescent Plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.

Regulatory History

COVID-19 convalescent plasma is plasma intended for transfusion that is collected from individuals who have recovered from COVID-19, which contains antibodies to SARS-CoV-2. COVID-19 convalescent plasma is a biological product subject to licensure under section 351(a) of the PHS Act. 42 U.S.C. 262(a). COVID-19 Convalescent Plasma is a blood component as defined in 21 CFR 630.3(b).

FDA first issued an Emergency Use Authorization on August 23, 2020, for COVID-19 convalescent plasma (CCP) for the treatment of hospitalized patients with COVID-19. FDA subsequently reissued the EUA with revisions. On December 28, 2021, FDA revised the EUA to limit authorization to the use of CCP with high titers of anti-SARS-CoV-2 antibodies for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment in either the outpatient or inpatient setting. At the time of the 2021 reissuance, the available studies in aggregate supported FDA's determination that that use of COVID-19 convalescent plasma with high titers of anti-SARS-CoV-2 antibodies may be effective in treating COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatment. In June 2024, FDA issued the guidance document "Recommendations for Investigational and Licensed COVID-19 Convalescent Plasma" (available https://www.fda.gov/media/180209/download and subsequently referred to as "CCP guidance" in this memo), which described FDA's considerations and recommendations for licensure of CCP. The recommendations included that sponsors should submit standard operating procedures that describe the criteria used to select donors, the processes to qualify CCP units, and a summary of safety and effectiveness information. FDA also recommended that, based on currently available clinical and scientific evidence, the indication for use for licensed CCP should be the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments. On December 10, 2024, FDA approved the first Biologics License Application (BLA) for COVID-19 Convalescent Plasma (https://www.fda.gov/media/184872/download) for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments. A review of the evidence supporting that BLA is available in the submission file(Ref.1). On August 27, 2025, considering that there was a licensed CCP product available and that the supply of licensed plasma was expected to meet clinical need, FDA revoked the EUA for CCP (https://www.fda.gov/media/188436/download) after determining that circumstances made revocation appropriate to protect public health or safety.

In the current submission, the sponsor has provided information consistent with the recommendations in the CCP guidance. The summary of safety and effectiveness provided in the current submission cites much of the same evidence used to support the EUA and the first licensed CCP product, and the assessment of those data can be found in the corresponding clinical review memoranda(Ref.1, 2). Herein, I review additional information provided by the sponsor, including the results of an additional prospective randomized controlled trial, and manufacturing information specific to the sponsor's approach to donor selection and product qualification.

Submission Contents

In the current submission, the sponsor provides information addressing the three key areas outlined in the June 2024 FDA CCP guidance:

- CCP summary of safety and effectiveness
    - Addressed in a memorandum dated 3/11/2025 with subject "Additional information regarding COVID-19 Convalescent Plasma (CCP)"
- Approach to donor and component qualification
    - Described in standard operating procedures and work aids
- Labeling (Circular of Information)
    - Provided for review and subsequently revised in response to FDA information requests

Clinical review of each of these key areas is discussed below.

Safety and Effectiveness Information

Safety

The sponsor includes information on the safety and effectiveness of CCP in pages 2-4 of the included memo. The sponsor cites safety data summarized in a book chapter by Joyner et al(Ref.3). This chapter describes adverse events reported during a national Expanded Access Protocol (EAP) sponsored by the Mayo Clinic (NCT04338360), which has also been extensively described in other published scientific literature(Ref.4), as well as a meta-analysis of published safety data from multiple prospective randomized studies (Ref.5). These data were considered in detail during review of the first licensed BLA for CCP and are also summarized herein. Under the EAP, more than 100,000 hospitalized subjects with severe of life-threatening COVID-19 were treated under expanded access, a portion of which were on immunosuppressive therapy (3.8%) or had potentially immunosuppressive comorbidities such as cancer (4.6%). The EAP was conducted under IND (b) (4) and detailed review of safety reports under the study can be found in the administrative file for that IND. Review of adverse events reported under the IND found that rates of adverse events associated with CCP transfusion were consistent with historical rates of adverse reactions associated with plasma transfusion in hospitalized patients with critical illness. The risks of CCP include those inherent to plasma transfusion such as transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), allergic/anaphylactic reactions, febrile non-hemolytic transfusion reactions, transfusion-transmitted infections, and hemolytic reactions. Specifically, in the EAP, rates of transfusion reactions are summarized in the figure and table below, adapted from Senefeld et al(Ref.4).

SAE	Possibly related	Probably related	Definitely related	Total	% (n=112,651)
Allergic transfusion reaction	8	21	81	**110**	0.10%
Febrile non-hemolytic transfusion reaction	15	22	10	**47**	0.04%
Hypotensive transfusion reaction	14	5	1	**20**	0.02%
TACO	56	95	12	**163**	0.14%
TRALI	22	14	2	**38**	0.03%
TACO/TRALI	105	110	1	**216**	0.19%
Other transfusion reaction	3	0	0	**3**	0.00%
Total	**223**	**267**	**107**	**597**	0.53%

A systematic review and meta-analysis of randomized controlled trials of CCP examined safety outcomes including any adverse reactions, serious reactions, treatment related adverse reactions, serious treatment related adverse reactions, and venous and arterial thrombotic events(Ref.5). The study included 39 randomized controlled trials enrolling 23,685 subjects. The study found no difference in any rates of any adverse reaction, any serious adverse reaction, serious treatment related adverse reactions, or venous and arterial thrombotic events between CCP treated subjects and controls. There was a slight increase in the rate of any treatment related adverse reaction of any grade (from 2.0% to 3.6%) when comparing CCP to control subjects. The sponsor and study authors attributed this difference to the use of placebo, as no difference was observed in this measure when comparing CCP to control subjects who received FFP. Similar patterns were observed in both the inpatient and outpatient setting. Overall, the incidence of treatment-related serious adverse events following CCP transfusion was low (0.5%) and consistent with data from the EAP summarized above. In review of data from large outpatient studies of CCP during assessment of the EUA, FDA analyses found that the rate of serious transfusion reactions in the outpatient studies was 0.4% overall (ranging 0-1.2% across the studies). This rate is very similar to those reported above.

Throughout the study of COVID-19 convalescent plasma, there has been theoretical concern regarding the potential for antibody dependent enhancement of disease(Ref.6) or suppression of host immune responses. As summarized in prior review memoranda for the CCP EUA(Ref.2), across several, large randomized controlled trials of CCP, there has been no clear clinical evidence of antibody dependent enhancement (ADE) of disease due to CCP transfusion or suppression of SARs-CoV-2 host responses or immunity(Ref.7). However, investigators in the CONCOR-1 study found that transfusion of CCP with unfavorable antibody profiles, such as non-functional, non-neutralizing antibodies may be associated with worse clinical outcomes compared to standard care(Ref.8). Other studies have not observed this phenomenon, and in CONCOR-1, this was only observed with CCP with much lower neutralization activity than that produced by the sponsor's proposed approach (see 'Qualification of CCP', below).

The sponsor also cites a small case series of 49 subjects treated with CCP reported by their institution which implemented an active surveillance protocol to monitor potential adverse reactions to CCP transfusion. In this series, a total of 49 patients received CCP. Seven patients (14%) experienced increased oxygen requirements within 4 hours of transfusion completion, including one patient who was intubated during the transfusion. 11 patients (37%) had increased oxygen requirements within 24 hours, 3 of which were intubated. They found that six patients (12%) met criteria for TACO. While active surveillance was able to capture transfusion associated adverse events, the authors described that it was not possible to definitively determine whether or not these adverse events were related to CCP transfusion, and assessed that TACO was likely over-diagnosed given overlap with the manifestations of COVID-19. They concluded that the potential adverse effects of CCP transfusion may be underestimated in passive surveillance data.

Overall, the sponsor concluded that "overall evidence strongly supports the safety of CCP and the risks of CCP transfusion do not appear to exceed those associated with plasma transfusion in general". Considering the rates of adverse events observed in multiple prospective randomized trials, and in more than 100,000 patients treated under the EAP, I agree with this assessment.

Effectiveness

The efficacy of CCP in the treatment of COVID-19 has been the subject of several randomized and non-randomized CCP clinical studies, as well as multiple meta-analyses, that have been previously considered in FDA's review of EUA(Ref.2) and the first licensure of CCP(Ref.1). The sponsor cites this same body of data in support of the effectiveness of CCP in the treatment of COVID-19 in the immunocompromised population. A more detailed consideration of those data is available in the corresponding clinical review memoranda. Those prior reviews concluded that CCP is effective in reducing progression to severe COVID-19 in certain populations, and that patients with immunosuppressive disease or receiving immunosuppressive treatments are likely to experience larger clinical benefit due to their higher risk for severe outcomes. Patients with immunosuppressive disease or receiving immunosuppressive treatments were also assessed as likely to have a longer therapeutic window due to impaired ability to generate humoral responses and slow viral clearance.

In addition to those data, the sponsor cites 2 observational studies from Ripoll et al of CCP use in the immunocompromised COVID-19 population(Ref.9, 10). In the first of these(Ref.10), investigators from the Mayo Clinic examined the use of vaccine-boosted CCP in 31 consecutive immunocompromised patients hospitalized with protracted COVID-19 between July 2021 and September 2022. The patient population had a median age of 63 years, with 68% having hematological malignancies, and had experienced COVID-19 symptoms for a median of 29 days before receiving vax-plasma treatment, despite prior therapies including remdesivir (97% of patients), steroids (84%), and neutralizing monoclonal antibodies (23%). Following CCP transfusion (median of 2 units per patient), the overall survival rate was 84% (26 of 31 patients), with 59% of inpatients (17 of 29) demonstrating rapid clinical improvement and hospital discharge within 5 days of treatment. The authors speculated that CCP appeared most beneficial in patients treated before requiring invasive mechanical ventilation. In the larger observational study(Ref.9), investigators examined the effectiveness of CCP in 386 immunocompromised COVID-19 outpatients at Mayo Clinic from December 2022 to December 2023, comparing outcomes between patients who received CCP plus standard care (225 patients) versus standard care alone (161 patients). The study

was a non-randomized observational cohort study design where all subjects were offered both standard-of-care treatments and CCP. The experimental arm included the 58% of subjects who accepted CCP transfusion, while the remaining 42% of patients who declined CCP served as controls. 73% of subjects received concomitant COVID-19-specific treatments, and subjects in the CCP arm were more likely to have received COVID-19-specific treatments (88%, 198 of 225 patients) compared to the standard-of-care group (52%, 83 of 161 patients; P < 0.001). COVID-19-specific treatments included remdesivir, nirmatrelvir and ritonavir, and/or molnupiravir. The study population had a median age of 66 years, was 45% female, and 94% were previously vaccinated against SARS-CoV-2. Subjects received a median of 1 unit of CCP after experiencing COVID-19 symptoms for a median of 5 days. The CCP arm experienced a significantly lower hospitalization rate of 2.2% (5 of 225 patients) compared to 6.2% (10 of 161 patients) in the standard-of-care group, representing a 65% relative risk reduction (P = 0.046). However, the non-randomized design and concomitant treatment imbalance limit the ability to make causal inference.

The sponsor also cites a case series from their institution on the use of CCP in 44 immunocompromised patients during the first omicron surge(Ref.11). This retrospective study examined the safety and outcomes of high-titer post-vaccine COVID-19 convalescent plasma (CCP) treatment in 44 hospitalized immunocompromised patients during the first omicron surge at Stanford Hospital between January and March 2022. The cohort included 59.1% solid organ transplant recipients, 22.7% hematopoietic cell transplant recipients, 11.4% with hematologic malignancy, and 6.8% with autoimmune disease. The CCP units were collected from recently recovered and vaccinated donors. The mean titer on Abbott AdviseDx SARS-CoV-2 IgG assay was 30,267 AU/mL in 17 units, while 3 units had titers above the upper limit of quantification (>50,000 AU/mL), and the only unit collected from an unvaccinated donor had a titer of 1293 AU/mL (the previous cutoff for high titer in this assay in the EUA was >1280 AU/mL). The treatment demonstrated acceptable safety with two mild transfusion reactions (4.4%, n=2, 1 febrile nonhemolytic reaction, 1 TACO requiring transient noninvasive supplemental oxygen). The 30-day all-cause mortality rate was 4.5% (2/44 patients, 1 septic shock with multiorgan failure, 1 brain herniation following stroke) and 100-day mortality of 15.9% (7/44 patients). The authors speculated that the mortality was lower than would be expected based on historical mortality rates reported for similar immunocompromised populations with COVID-19 and concluded that “High-titer post-vaccine CCP was shown to be safe for immunocompromised patients admitted to the hospital for COVID-19 in the era of omicron. Thirty-day mortality was low.”.

The sponsor also cites results of the COVIC-19 study(Ref.12). COVIC-19 was a prospective, randomized, controlled, open-label trial (COVIC-19) investigating the efficacy of high-titer CCP in 120 immunocompromised patients with mild COVID-19 across 10 centers in Germany, France, and the Netherlands. The study population was immunocompromised patients (mostly organ transplant recipients [~75%], hematologic malignancy [~19%], and allogeneic HSCT [~3%]) with mild COVID-19 within 7 days of symptom onset. Notably, subjects had mostly been vaccinated 3 or more times (>90% of subjects) and most (87%) also received concomitant anti-SARS-CoV-2 therapies including monoclonal antibodies and antivirals. Subjects were randomized to either standard of care alone or standard of care plus two units of CCP (median 559 mL) from vaccinated, convalescent donors with high SARS-CoV-2 antibody concentrations. CCP contained >4000 BAU/mL (Euroimmun Quantivac assay), >20,000 IU/mL (Roche Elecsys assay), or a neutralizing titer of at least 1:640 against delta, omicron, or other future variant. CCP was administered at a median of 4 days after symptom onset. The primary outcome of hospitalization for progressive COVID-19 symptoms or death by day 28 occurred in 5/58 patients (8.6%) in the standard of care group compared to 0/59 patients (0%) in the CCP group, representing a difference of -8.6% (95% CI -19% to -0.80%; p=0.027). Events were adjudicated as COVID-19 related by a blinded committee. The effect was larger in subjects who had not received prior monoclonal antibody therapy. Serious adverse events were less common in the CCP arm (20%) compared to the SoC arm (36%). On day 3 of follow up, antibody titers, including neutralization testing, were higher in the CCP arm compared to SoC controls. This study provides well-controlled evidence of the effectiveness of CCP in the treatment of COVID-19 directly in the population of patients with immunosuppressive conditions or receiving immunosuppressive therapy.

Donor and Component Qualification

The sponsor provided information on donor and component qualification on pages 1-2 on the included memorandum and pages 1-2 of a document titled “15-STUDY-22, COVID-19 Convalescent Plasma Work Aid”. In order to qualify for collection of CCP, donors must have had symptomatic COVID-19 in the past 6 months, evidence of a positive diagnostic test (either direct or based on MD review of the donor’s medical history), and a history of vaccination for SARS-CoV-2. For the donation to be suitable for labeling as CCP, the donation must have a test result of at least 1280 AU/mL on the Abbott AdviseDx SARS-CoV-2 IgG II semi-quantitative assay. This test is FDA authorized for the qualitative and semi-quantitative detection of anti-SARS-CoV-2 antibodies (EUA203119) and this test was previously included in the CCP EUA as an acceptable manufacturing test for high-titer CCP. Using this assay and the sponsor’s approach to donor selection, CCP collected at Stanford Blood Center (SBC) in 2024 had a mean titer of 35,913 AU/mL, with a minimum of 11,588 AU/mL. Although this test is FDA authorized for semi-quantitative detection of anti-SARS-CoV-2 antibodies and provides results in arbitrary units (AU), the relationship of the assay results to WHO international standards has been described in published scientific literature(Ref.13), with a conversion factor to WHO binding antibody units (BAU) of 1 BAU/ml to 0.142 AU/mL. Therefore, the mean antibody titer using the SBC approach to donor qualification was roughly 5,099 BAU/mL, with a minimum of 1645 BAU/mL. As a comparison to previously licensed CCP, CCP manufactured by the currently licensed establishment using their approach to donor selection and product qualification resulted in a geometric mean titer of ~4758 BAU/mL, and thus, the two establishments’ approaches result in CCP of similar titer. Therefore, the sponsor’s approach to donor selection and antibody testing is acceptable, very likely to provide high titer products that minimize the risk of suboptimal antibody composition, and exceeds the cutoffs used in several studies of CCP and those previously authorized under EUA.

A recent publication further described the approach used for product collection in the COVIC-19 study(Ref.14). Donors for that study had a history of both SARS-CoV-2 infection and vaccination, which is similar to the sponsor’s proposed approach. Of 688 potential donors screened between November 2021 and March 2023, 41.4% met the high titer threshold, with the highest titers observed in individuals who experienced breakthrough infection after two vaccinations followed by a booster (median 5374 BAU/mL) or breakthrough infection after the 3rd or 4th vaccination (median 3846 BAU/mL). Ultimately, 172 eligible individuals donated CCP through 450 plasmapheresis sessions, producing 857 compliant units with a median concentration of 6858 BAU/mL that demonstrated broad cross-neutralization against multiple SARS-CoV-2 variants including B.1, BA.1, BA.2, and BA.5, though neutralization capacity was significantly reduced against newer variants like XBB.1.5 and BQ.1.1.

Circular of Information (COI)

The sponsor has provided an addendum to the FDA-recognized Circular of Information for the Use of Human Blood and Blood Components(Ref.15) that includes:

- Indications
- Administration/Dosing
- Description of the Product and Donor Qualifying Criteria
- Side Effects and Hazards

Initial review of the sponsor’s proposed COI found that the product description lacked specific information, including that donors had recovered from symptomatic COVID-19 in the last 6 months, and the specific test and cutoff used to qualify the titers (result of at least 1280 AU/mL in AdviseDx SARS-CoV-2 IgG II). In addition, the dating period was not stated. The ‘Side Effects and Hazards’ described theoretical risks of ADE and immune suppression, that had not been demonstrated in well-controlled studies and, therefore, it was judged that the statements should be removed from the COI. Finally, the labeling lacked a contraindication statement in patients with known hypersensitivity. These deficiencies in the labeling were communicated to the sponsor through information requests, and the sponsor has provided a revised addendum to the FDA-recognized COI(Ref.15). Taken together, these documents provide adequate directions for use and meet the requirements of 21 CFR 606.122.

Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• COVID-19, caused by SARS-CoV-2 infection, can cause serious illness including respiratory disease, thromboembolic events, cardiomyopathy, neurologic injury, among others. • Immunocompromised patients are at higher risk for severe adverse outcomes after SARS-CoV-2 infection. • SARS-CoV-2 continues to circulate widely in the US and hospitalizations and deaths due to COVID-19 continue to occur, although decreased from pandemic highs. • Vaccination and anti-viral therapies are important for prevention and treatment of COVID-19. • SARS-CoV-2 variants continue to emerge, and while prior immunity due to vaccinations and prior infection remain protective against severe outcomes, the potential for variants capable of escaping immunity remains.	• COVID-19 remains a significant health risk, and SARS-CoV-2 is likely to continue to circulate in the population leading to new variants. • Patients with immunosuppressive disease or receiving immunosuppressive treatments at risk for more severe adverse outcomes and CCP may be an important aspect of their treatment.
Unmet Medical Need	• Although passive immune therapies, such as monoclonal antibodies, were previously shown to be safe and effective and were authorized for treatment of COVID-19, the emergence of variants has resulted in the loss of antibody activity against circulating SARS-CoV-2 strains. • Other treatments (such as small molecule antivirals) are available but may fail to completely clear virus in immunocompromised hosts. • Oral therapies are more readily implemented in clinical practice, but some antiviral therapies (nirmatrelvir/ritonavir) may be limited by their interaction with other medications. • No anti-SARS-CoV-2 hyperimmune globulin product is currently available in the US.	• There is unmet medical need for effective treatment of SARS-CoV-2 in immunocompromised patients. • Because high-titer, polyclonal CCP is more likely to retain neutralization activity compared to monoclonal antibody products, and CCP from recently infected individuals is more likely to contain antibodies specific to circulating strains, CCP remains a potentially important therapeutic option for immunocompromised patients.
Clinical Benefit	• High-titer CCP is likely to be effective in reducing mortality and the risk of severe COVID-19 when administered early in the course of illness. • High-titer CCP reduced the risk of COVID-19 related hospitalization or death in a prospective randomized trial of CCP in immunocompromised patients. • In patients with immunosuppressive disease or receiving immunosuppressive treatments, high-titer CCP appears to improve viral clearance and have a longer therapeutic window for clinical benefit. • Polyclonality of high-titer CCP, and earlier clearance of SARS-CoV-2 may mitigate the emergence or persistence of resistant variants in patients with immunosuppressive disease or receiving immunosuppressive treatments.	• CCP is effective in reducing progression to severe COVID-19 in certain populations. • Patients with immunosuppressive disease or receiving immunosuppressive treatments are likely to experience larger clinical benefit due to their higher risk for severe outcomes. • Patients with immunosuppressive disease or receiving immunosuppressive treatments are likely to have a longer therapeutic window due to impaired ability to generate humoral responses and slow viral clearance.
Risk	• Plasma transfusion is known to have a low rate of transfusion reactions, including allergic reactions, TACO, and TRALI, among others (~0.5-1%). • There were no safety signals for increased risk of thrombotic events due to CCP in well-controlled studies. • There is no clear evidence of antibody dependent enhancement of disease or suppression of host immune responses with high-titer CCP. • In studies of CCP, transfusion reaction rates for CCP were similar to control plasma and historical rates for plasma transfusion in other settings. • CCP may contain low titers or lack cross-reactivity against circulating variants without adequate approaches to donor selection and product qualification.	• CCP has similar risks to conventional plasma for transfusion. • The low risk of transfusion reactions due to CCP transfusion is more likely to be acceptable when there is a significant risk of severe COVID-19. • Risks of severe COVID-19 in immunocompromised patients are likely to outweigh the low risk of transfusion reactions.
Risk Management	• Transfusion reactions are routinely monitored and reported in clinical practice • Individuals with a history of both infection and vaccination are more likely to have higher neutralization titers and better retention of cross-variant neutralization	• Standard operating procedures for blood component transfusions are adequate to manage the risk of transfusion reactions • The sponsor's approach to donor selection and neutralizing antibody testing is very likely to provide high titer products that minimize the risk of suboptimal antibody composition

Recommendation

I recommend approval of BLA 125396/21 for licensure of COVID-19 Convalescent Plasma for the treatment of COVID-19 in patients with immunosuppressive disease or receiving immunosuppressive treatments.

References

1. *BLA 101766/5169 - Clinical Review Memorandum.* Available from: https://www.fda.gov/media/188795/download.
2. *COVID-19 Convalescent Plasma Emergency Use Authorization - Clinical Review Memorandum.* Available from: https://www.fda.gov/media/155159/download.
3. Joyner, MJ, et al., *The Safety Profile of COVID-19 Convalescent Plasma.* Curr. Top. Microbiol. Immunol., 2024.
4. Senefeld, JW, et al., *Access to and safety of COVID-19 convalescent plasma in the United States Expanded Access Program: A national registry study.* PLoS Med., 2021. **18**(12): p. e1003872.
5. Franchini, M, et al., *Safety of COVID-19 convalescent plasma: A definitive systematic review and meta-analysis of randomized controlled trials.* Transfusion, 2024. **64**(2): p. 388-399.
6. Coish, JM, LA MacNeil, and AJ MacNeil, *The SARS-CoV-2 antibody-dependent enhancement façade.* Microbes and Infection, 2025. **27**(3): p. 105464.
7. Chan Andy Kwan, P, et al., *The effect of early COVID-19 treatment with convalescent plasma on antibody responses to SARS-CoV-2.* Microbiology Spectrum, 2025. **13**(7): p. e03006-24.
8. Bégin, P, et al., *Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial.* Nat. Med., 2021. **27**(11): p. 2012-2024.
9. Ripoll, JG, et al., *Outpatient treatment with concomitant vaccine-boosted convalescent plasma for patients with immunosuppression and COVID-19.* mBio, 2024. **15**(5): p. e0040024.
10. Ripoll, JG, et al., *Vaccine-boosted convalescent plasma therapy for patients with immunosuppression and COVID-19.* Blood Advances, 2022. **6**(23): p. 5951-5955.
11. Tayyar, R, et al., *High-titer post-vaccine COVID-19 convalescent plasma for immunocompromised patients during the first omicron surge.* Transpl. Infect. Dis., 2023. **25**(2): p. e14055.
12. Hoffmann, S, et al., *Early, very high-titre convalescent plasma therapy in clinically vulnerable individuals with mild COVID-19: an international, randomised, open-label trial.* eBioMedicine, 2025. **113**.
13. Maine, GN, et al., *Clinical and analytical evaluation of the Abbott AdviseDx quantitative SARS-CoV-2 IgG assay and comparison with two other serological tests.* J. Immunol. Methods, 2022. **503**: p. 113243.
14. Hoffmann, S, et al., *SARS-CoV-2 convalescent plasma for the controlled clinical trial "COVIC-19": Experience from collection of very high-titer plasma from superimmunized individuals.* Transfusion, 2025.
15. *An Acceptable Circular of Information for the Use of Human Blood and Blood Components.* 2022. Available from: https://www.fda.gov/media/86898/download.