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REVIEW

TRANSFUSION

Regulatory challenges of convalescent plasma collection during the evolving stages of COVID-19 pandemic in the United States

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1 | GLOBAL HEALTH CRISIS OF COVID-19

December 2019 marked a watershed for global health when a large number of patients presenting with severe respiratory symptoms were hospitalized in Wuhan, China. Some patients (about 5%) developed acute respiratory distress syndrome and had a rapidly deteriorating clinical course, in spite of intensive care and ventilatory support.[1,2] Nasopharyngeal swabs revealed a novel coronavirus that was different in epidemiological, clinical, and molecular features from coronaviruses that caused outbreaks of severe acute respiratory syndrome (SARS-1) in 2003 and Middle Eastern respiratory syndrome (MERS) in 2012.[2] Within just a few weeks after December 2019, cases were found in increasing numbers in European countries and the United States. On February 4, 2020, coronavirus disease 2019 (COVID-19) was declared a public health emergency in the United States by Health and Human Services (HHS). By February 24, 2020, more than 80,000 confirmed cases and more than 2700 deaths had been reported affecting at least 37 countries.[3] On March 11, 2020, it was characterized as a pandemic by the World Health Organization (WHO).

2 | CONVALESCENT PLASMA: THE ONLY TREATMENT OPTION

Since there were no evidence-based therapeutic and preventive options available,[4] clinical trials of existing therapeutics including remdesivir, chloroquine, hydroxychloroquine, lopinavir, and ritonavir to treat COVID-19 were emergently started.[5] COVID-19 convalescent plasma (CCP) was considered a viable and possibly useful therapeutic based upon the past treatment of respiratory viral diseases.[6] Hence, the trials were started, and the initial case series reports involving a small number of patients were suggestive of a potential benefit.[7,8] Due to historic data regarding the safety and

Abbreviations: ACE2, angiotensin converting enzyme 2; BARDA, biomedical advanced research and development authority; CCP, collected convalescent plasma; EAP, expanded access treatment protocol; eIND, emergency investigational new drug; EUA, emergency use authorization; FD&C, federal food, drugs and cosmetics act; FDA, US food and drug administration; HHS, US department of health and human services; IDSA, infectious diseases society of america; MERS, middle eastern respiratory syndrome; NS3, national SARS-COV-2 strain surveillance; PRNT, plaque reduction neutralization test; RBD, receptor binding domain; SARS, severe acute respiratory syndrome; S/C, signal to cut-off; WHO, World Health Organization.

efficacy of convalescent plasma use in other respiratory diseases and new data from preclinical and early clinical studies, FDA began granting requests for emergency single patient investigational new drug (eIND) applications in late March, 2020, and issued guidance for CCP use as an IND in April, 2020.[5,9] FDA sanctioned an alliance between major blood suppliers, the Mayo Clinic, and transfusion services to create the National Expanded Access Treatment Protocol (EAP). The EAP permitted the use of CCP in patients without having to apply for an IND for each patient.[10] FDA-licensed blood collection establishments across the United States faced a drastic, emergent challenge and started collecting CCP from qualifying donors on a large scale, as COVID-19 cases continued multiplying.[11,12]

Convalescent plasma had been used in viral epidemics of SARS-1, H1N1 influenza virus,[13] Ebola[14,15] and MERS with favorable results in some studies, though most published studies were performed on a small number of patients and were nonrandomized. Historically, it was also reported to benefit patients during the influenza pandemic in 1918[4,16] and to significantly reduce fatality in patients of Argentine hemorrhagic fever, if used early in the course of disease.[17,18] On April 24, 2020, WHO guidance mentioned lack of enough evidence to guarantee that having antibodies insured immunity against SARS-CoV-2.[19] Even though evidence was insufficient, CCP was considered modestly important and one of the only small number of potentially effective treatment options due to its historic use, safety, and lack of alternate options.[6,19]

3 | FDA REGULATIONS BASED UPON EMERGING EVIDENCE

On March 27, 2020, HHS declared that circumstances existed that justified the emergency use of drugs and biological products pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act (Figure 1).

3.1 | FDA initial guidance

In April, 2020, FDA issued guidance for CCP collection as an IND,[20] and its administration under IND application used three pathways, that is, traditional IND for regulatory clinical trials, using the EAP, or single patient eIND for patients hospitalized with COVID-19.[20] In early April, Mayo clinic initiated the EAP under funding from Biomedical Advanced Research and Development Authority (BARDA), whose primary goal was to provide CCP to hospitalized patients and determine its safety and secondarily explore the efficacy of CCP.

During the initial few months of the pandemic, no validated and feasible SARS-CoV-2 antibody assays were available. As a result, CCP donor eligibility criteria did not require antibody testing of the units.[20] Per FDA guidance in April, 2020, CCP was collected from donors having a history of COVID-19 (determined either by molecular test or positive serology for SARS-CoV-2) and >28 days after the resolution of symptoms or >14 days after the resolution of symptoms along with negative molecular test for SARS-CoV-2 on a nasopharyngeal specimen. FDA guidance recommended neutralization antibody testing of CCP units, but it was not required.[20] If the antibody testing could not be performed in advance, testing of CCP retention vials at a later time was recommended. Blood establishments were neither required to have a supplement to their FDA license for CCP collection nor required to collect under a separate IND protocol, if they followed their standard procedures of plasma collection from qualified donors.[20] The guidance specified that labeling of a CCP unit must state,

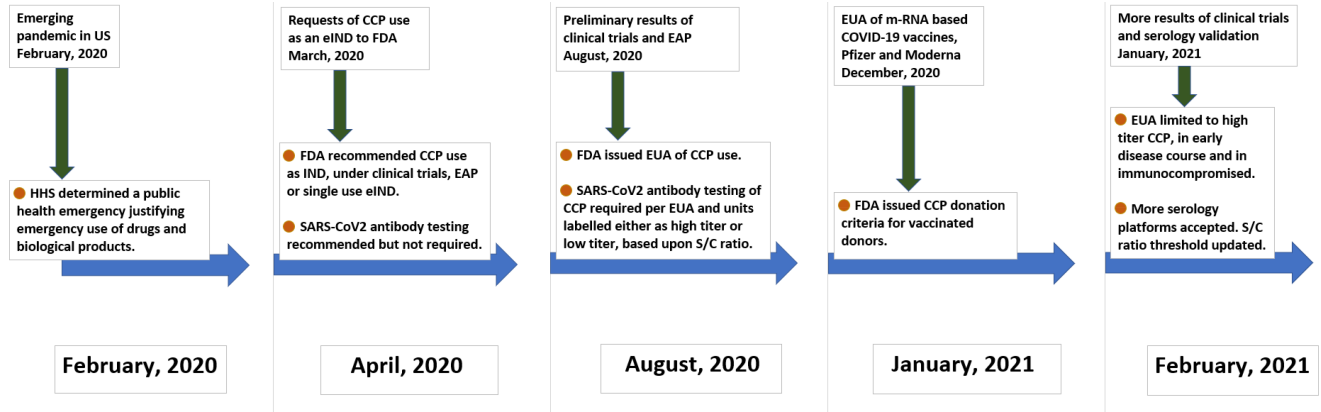

FIGURE 1 Salient updates of Food and Drug Administration (FDA) guidance during the evolving stages of coronavirus disease 2019 (COVID-19) pandemic, showing the major developments during the pandemic along with their respective FDA regulatory updates [Color figure can be viewed at wileyonlinelibrary.com]

"New Drug: Limited by Federal law to investigational use." Labeling was also required to include recognition that the current circular of information does not include information about CCP indication, dosage, and contraindications, but it provided information about the use of plasma. FDA guidance also recommended that the CCP manufacturing process and its expiration date on the label should be the same as of any other plasma manufactured and stored by the same method. Due to logistical problems with timely availability of neutralization antibody test results, titers of neutralizing antibodies of CCP units were unknown at the time of transfusion in many cases, a significant factor in studies that was met by criticism later.[20]

On April 24, 2020, FDA issued emergency use authorization (EUA) for the Ortho VITROS anti-SARS-CoV-2 IgG test for SARS-CoV-2 IgG antibody detection by -CLIA-certified laboratories, after data about its performance became available.[21] Ortho VITROS anti-SARS-CoV-2 IgG was a qualitative test that used a chemiluminescent technique for detecting anti-SARS-CoV-2 IgG.[21] Subsequently, more data about antibody test performance became available and showed a correlation between certain semiquantitative anti-SARS CoV-2 IgG immunoassays and viral neutralizing antibody titers.[22–25] As of October 5, 2021, FDA has issued individual EUA to 89 serology testing platforms that detect SARS-CoV-2 IgG, IgM, both IgG and IgM, total antibody (IgA, IgM, and IgG), quantitative IgG or total neutralizing antibodies, after evaluating their performance in independent validation studies.[26]

3.2 | Emergency use authorization

On August 23, 2020, FDA determined that the use of CCP in hospitalized patients with COVID-19 met the "may be effective" criterion for issuance of EUA per section 564(c) (2)(A) of the FD&C Act and, therefore, issued EUA for CCP treatment of hospitalized COVID-19 patients (Table 1).[27] Following the EUA issuance, the CCP treatment under nationally available EAP was discontinued on August 28, 2020.[28] EUA for CCP was based upon historical evidence from use of convalescent plasma in respiratory viral infections, data from preclinical studies, data from early clinical trials, and the preliminary data from EAP.[29,30] EAP findings from the initial 20,000 cases treated with CCP showed it was as safe as regular plasma with a low overall frequency of serious adverse events within 4 hours of the completion of transfusion (<0.1% of all transfusions).[31] Efficacy analyses correlating neutralizing antibody titer to the observed clinical outcome were performed on 4330 recipients of CCP. Antibody levels were determined using Broad Institute SARS-CoV-2 neutralizing assay, Mayo Clinic pseudovirus neutralization assay and Ortho VITROS IgG assay as described below.

At the time of EUA, there were no validated assays for quantification of neutralizing antibodies titer in CCP. Three assays were described in the EUA submission request, and FDA/CBER separately received data from a set of CCP samples to compare those assays.[32] The three assays studied were Broad Institute SARS-CoV-2 neutralization assay, Ortho VITROS anti-SARS-CoV-2 IgG assay, and Mayo Clinic pseudo virus neutralization assay. Although their performance comparison with the gold-standard plaque reduction neutralization test (PRNT) was not available at the time of EUA, the three assays correlated well with each other.[32] Based upon the available evidence, Broad Institute neutralization assay was considered as the reference, since it used the native SARS-CoV-2 virus to determine the titer needed for 50% inhibition of the infection of cultured cells (ID50 titer).[32] No difference in 7-day mortality was seen in the CCP treated overall population and the intubated patients using Broad Institute neutralization assay ID50 titer of either ≥250 or <250. However, in nonintubated patients, there was a 21% reduction in 7-day mortality from 14% to 11% ($p = .03$) in patients treated with CCP with Broad Institute neutralizing assay ID50 of ≥250, as compared to nonintubated patients who were transfused CCP with lower titers. Hence, favorable results were observed with high-titer CCP treatment using Broad Institute neutralization assay ID50 cut-off of 250 and only early in the course of disease. Cross-laboratory titer comparison study showed Ortho VITROS SARS-CoV-2 IgG serum to cut-off (S/C) ratio of 12.0 correlated with Broad Institute neutralization ID50 titer of 250.[32] Hence, the FDA EUA specified the requirement of SARS-CoV-2 antibody testing of all CCP units by Ortho VITROS anti-SARS-CoV-2 IgG assay with S/C ratio of ≥12.0 for qualification as a high-titer CCP unit, as a part of manufacturing process and required clear labeling instructions of units, either as high titer or low titer. Low-titer units were defined by S/C ratio of <12.0 as tested by Ortho VITROS. Other testing platforms required prior CBER approval and an EUA amendment.[27] The FDA guidance recommended clinical dosing and rate of administration based upon the physician's judgment, while considering patient response and risk factors for fluid overload.[27]

In August 2020, EAP preliminary results showed a significantly better 7-day and 28-day survival in non-intubated, hospitalized patients treated with high-titer CCP transfusion than those treated with low-titer CCP transfusion.[9,29] However, there was no control arm for patients not treated with CCP. FDA issued an updated

TABLE 1 Important landmarks in COVID-19 convalescent plasma collection

Date	Intervention	Update	Authorized setting	Comments
February 04, 2020		HHS determined a public health emergency		HHS determined that a public health emergency exists with a potential to affect health of US citizens.
March 27, 2020	Emergency use of drugs or biological products			HHS declared that the emergency justifies the emergency use of drugs/biological products.
April, 2020	CCP	FDA guidance about use as IND	Hospitalized patients, including patients with severe disease	CCP use under clinical trials, EAP, or single use eIND. No validated antibody assays. Neutralizing antibody test recommended but not required.
April 24, 2020	Serology, IgG SARS-CoV-2	EUA of SARS-CoV-2 IgG assay	Labs performing high and moderate complexity tests	EUA granted to Ortho VITROS IgG assay and later to other platforms.
August 23, 2020	CCP	EUA: Units to be labeled either as high titer or low titer	Hospitalized patients	High-titer units had IgG SARS-CoV-2 S/C ratio of ≥12 and low-titer unit S/C ratio of <12, as tested by Ortho VITROS. Clinical trials not to be amended.
September 23, 2020	CCP	EUA Update: Continuation based upon the updated evidence	Hospitalized patients	EAP: Better 7-day and 28-day survival in nonintubated patients treated with high-titer than low-titer units; no control arm
September, 2020	CCP	Temporary enforcement discretion for units collected before EUA	Hospitalized patients	Temporary discretion for CCP use without specified antibody testing, as IND, for 90 days.
January 15, 2021	CCP	EUA Update: Criteria for vaccinated donors. Temporary enforcement discretion extended.	Hospitalized patients	EUA of mRNA based COVID-19 vaccines in December, 2020: Criteria for vaccinated donors defined. Temporary discretion for CCP without specified antibody test, as IND, till May 31, 2021.
February 04, 2021	CCP	EUA Update: High-titer units only. More serology platforms. Ortho VITROS IgG S/C ratio revised.	Hospitalized patients, early in the course of disease and in immunocompromised patients.	More testing platforms accepted and their respective S/C ratios specified. Ortho VITROS IgG S/C ratio threshold for high-titer unit changed from ≥12.0 to ≥9.5.

Abbreviations: CCP, COVID-19 convalescent plasma; EAP, expanded access program; eIND, emergency investigational new drug; EUA, emergency use authorization; FDA, Food and Drug Administration; FD&C, Food, Drugs and Cosmetics Act; HHS, Health and Human Services; S/C ratio, sample to cut-off ratio.

review of EUA describing the available evidence and lack of control arm in EAP on September 23, 2020.[9] The review determined that CCP continued to meet the criteria of EUA based upon updated evidence but strongly encouraged the continuation of randomized controlled trials (Table 1).[9]

After EUA in August 2020, FDA received multiple inquiries about the products that had already been collected as IND without anti-SARS-CoV-2 testing or the need to continue to collect CCP, while operational changes were being made to meet the antibody testing requirements set forth in EUA.[28] To be able to use CCP units without knowing the antibody titers, in September, 2020, FDA allowed a temporary "enforcement discretion" concerning the administration of CCP units under investigational use, which was twice extended through the end of May, 2021,[28] to permit blood collectors to have FDA-approved titer testing in place. However, FDA recommended testing for neutralizing antibody titers, when available.[28]

3.3 | FDA guidance about vaccinated donors

On December 11, 2020, FDA granted EUA to Pfizer-BioNTech COVID-19 Vaccine[33] and on December 18, 2020, FDA issued EUA to Moderna COVID-19 Vaccine,[34] to be distributed and administered in the United States. As a result, FDA issued guidance on January 15, 2021, addressing the questions about qualification of vaccinated CCP donors. Donors who were vaccinated but had no history of COVID-19 infection were not eligible to donate CCP. The revised document deemed a donor eligible if the donor had received an investigational or licensed vaccine after the diagnosis of COVID-19 and was within 6 months after the complete resolution of their COVID-19 symptoms.[28]

On February 4, 2021, FDA revised the EUA based upon updated evidence and published results of clinical trials.[35] Based upon the available data, potential benefit was observed with administration of high-titer units, early in the course of disease, that is, before the respiratory failure. The revised EUA included patients with suppressed humoral immunity due to lack of sufficient studies on such patients. As a result, the revision restricted the use of CCP to only high-titer units in hospitalized patients early in the course of disease or those hospitalized patients with impaired humoral immunity.[28] The use of low-titer unit under EUA was no longer authorized. The revision also added additional platforms of anti-SARS-CoV-2 testing as acceptable and specified titer cut-off values for each of those platforms, for qualification of each unit as of high titer. In addition, it also changed the titer cut-off of Ortho VITROS SARS-CoV-2 IgG from S/C $\geq$ 12.0 to S/C $\geq$ 9.5, in order to qualify as a high-titer unit (Figure 1).[35]

On February 11, 2021, the guidance maintained the eligibility criteria for vaccinated donors to donate CCP but also described the criteria for individuals who had received an investigational COVID-19 monoclonal antibody therapy. Those individuals were considered ineligible for donation until at least 3 months after receiving the monoclonal antibody treatment, in order to ensure the CCP contains antibodies as a result of COVID-19 infection and not just the monoclonal antibodies.[28]

4 | COVID-19 CONVALESCENT PLASMA TREATMENT EFFICACY: UPCOMING CHALLENGES

4.1 | Summary of evidence

After more than one and a half years since the pandemic started, there is no available standard of care treatment. As of October 5, 2021, the United States had 43,896,761 reported cases and 704,271 deaths due to the disease.[36] Clinical trials have addressed safety[31,37] of CCP, but they have mixed results and study limitations about the efficacy.[7,29,30,38–41] The largest criticism of most trials to date is their lack of randomization. See Appendix S1.

In two recent randomized controlled trials of hospitalized patients, no significant difference in 1-month mortality between the treatment arm with high-titer CCP and the control arm was observed.[42,43] In another randomized trial conducted in the United States and Brazil, including 150 patients who received CCP and 73 patients who received normal plasma, a significant lowering of the 28-day mortality was seen in the CCP arm (12.6%) as compared to the control arm (24.6%). Genomic sequencing of a subset of 40 specimens of patients from Brazil showed no neutralization escape mutants (no specimen had B.1.1.28 P1 mutation) (74).[44] To date, only high-titer CCP has been shown to have a possible survival benefit, if transfused early in the course of disease. As of June 3, 2021, the Infectious Diseases Society of America (IDSA) recommends against the use of CCP in hospitalized patients. The guideline panel recommended CCP for ambulatory patients only in the context of a clinical trial.[45] IDSA did not recommend "for or against" CCP transfusion in ambulatory patients and immunocompromised patients.[45]

Clinical trials are needed in patients with mild symptoms, in order to determine if the treatment prevents progression to severe symptoms. In a randomized, double

blind, placebo controlled trial of older patients with mild symptoms, high-titer CCP treatment within 72 hours of symptom onset resulted in 16% progression to severe respiratory disease, as compared to 31% progression in placebo control, though it had limited statistical power and lacked long-term outcome.[46] Efficacy data in specific patient populations with various comorbidities are also limited. A few cases have been reported for CCP use in immunocompromised patients with favorable outcomes, and most of them described a benefit with high-titer units.[47–51] The FDA EUA update (on February 4, 2021), that limited CCP transfusion under EUA to high-titer unit only, described the lack of studies in patients with compromised humoral immunity and, hence, recommended the use of high-titer units only in hospitalized patients early in the course of disease and in those hospitalized patients with suppressed humoral immunity.[28] A subsequent case series of 14 immunocompromised patients, with the mean time to transfusion of 5.14 days after a positive SARS-CoV-2 PCR result, showed a favorable outcome in 12 patients.[47] The role of convalescent plasma in postexposure prophylaxis of hepatitis, polio, rabies, measles, and mumps is known,[52] but the same needs to be investigated after exposure to SARS-CoV-2.[11] At this time, postexposure prophylaxis using monoclonal antibody therapy is authorized by FDA. In the original EUA guidance and in each subsequent update, FDA emphasized that the ongoing clinical trials of CCP use as IND should not be amended based upon the issuance of EUA[27,28,35] and underscored the importance of further enrolment of patients in those trials.[35]

4.2 | Lessons for the future

A major limitation in the larger studies is a lack of a randomized control arm.[39,40] Randomization in the EAP did not become possible because the primary goal of the EAP was to assess safety and facilitate CCP access to hospitals across the United States, that were overwhelmed with patients during a pandemic but did not have infrastructure for randomized trials. Moreover, randomization required subject willingness to be randomized into treatment arm or placebo arm that was probably influenced by the popular thought and the historical evidence of benefit of convalescent plasma use in other viral illnesses.[29] For future life-threatening pandemics or variant outbreaks, efforts should focus on optimal study designs, in addition to ensuring safety and access to investigational treatments. For treatment of immunocompromised patients with investigational immunotherapy, randomized trials should be conducted early during the pandemic.

4.3 | Efficacy after vaccination

Favorable results of vaccine trials (>90% efficacy of some vaccines at preventing infection) provided hope and the beginning of vaccinations in the United States in December, 2020, was a historic moment. A major question about vaccinated donors is the efficacy of CCP collected from those donors. A recent study suggested that individuals with history of COVID-19 infection 1–2 months before vaccination show higher anti-SARS-CoV-2 IgG levels than vaccinated individuals who did not have prior COVID-19.[53] On January 15, 2021, FDA guidelines specified the CCP donor qualification criteria for vaccinated donors, and they were deemed eligible under EUA only if they had received an investigational or licensed vaccine after the diagnosis of COVID-19 and were within 6 months after the resolution of COVID-19 symptoms.[28] This was meant to ensure that for transfusion of CCP under EUA, the donors contain antibodies as a result of immune response directly against SARS-CoV-2 infection.[28] The guidance also stated that administration of vaccine for the purpose of boosting the immunity of CCP donors must be conducted within a clinical trial under IND (21 CFR Part 312).[28] Another question is the efficacy of CCP collected from donors who received the vaccine before developing COVID-19 disease due to breakthrough infection, vaccination failure, or decreasing antibody levels. Efficacy of CCP in vaccine recipients who would possibly contract infection after getting vaccinated, due to waning antibody levels or vaccination failure, remains to be investigated.

4.4 | Efficacy against variants

Earlier in the pandemic, the D614G mutation in SARS-CoV-2 was found to be associated with high infectivity, and it was the predominant global strain by June, 2020.[54–56] The coronavirus genome is highly susceptible to mutations, resulting in genetic drift that may escape immune recognition.[57] Emergence of a new SARS-CoV-2 variant B.1.1.7 in the United Kingdom, B.1.351 in South Africa and P.1 in Brazil posed new challenges but were downgraded from WHO category "variants of concern" to the category "variants being monitored," on September 21, 2021.[58]

A study compared the viral neutralization of patients infected during the first wave of the pandemic in South Africa with the viral neutralization of patients infected with 501Y.V2 (also known as B.1.351) variant in South Africa. Sequencing of specimens from the first wave of infection did not show mutations associated with 501Y.V2, unlike were observed during the second wave.

Viral neutralization of 501Y.V2 was effective with CCP collected from patients infected during the second wave, but its neutralization was 15.1 folds less than with CCP collected during the first wave. However, cross-neutralization of SARS-CoV-2 from patients infected during the first wave using CCP from individuals infected during the second wave was more effective and showed only a 2.3-fold decrease as compared to CCP collected during the first wave.[59] In another study performed in Germany, CCP samples were collected when the spread of the B.1.1.7, B.1.351, and P.1 variants was very limited there. The CCP samples were prescreened for neutralizing activity against the S protein of wild-type SARS-CoV-2. The samples inhibited the S protein of B.1.1.7 slightly less efficiently as compared to the S protein of wild type. However, seven out of the nine CCP samples inhibited S proteins of B.1.351 and P.1 considerably less efficiently as compared to wild-type S protein, suggesting that individuals infected with wild-type SARS-CoV-2 might only be partially immune to B.1.351 and P.1 variants.[60] An in vitro study using high-titer CCP showed that the plasma neutralized the virus initially for seven passages, followed by generation of a variant at 80 days, that was completely resistant to neutralization by the CCP.[61] A study in December, 2020, suggested evolution of SARS-CoV-2 variant B.1.1.7 by escaping through CCP treatment of a patient.[62] However, a statement from National Health Service, UK, denounced the speculation in January, 2021, and stated that there is no such evidence.[63] A study demonstrated neutralization of a panel of SARS-CoV-2 variants, including the B.1.1.7 variant with sera obtained from acutely infected patients, convalescent individuals, and mRNA-based vaccinated individuals, using a live virus focus reduction neutralization assay. Neutralization titers for the variants (that included the B.1.1.7 variant) correlated with one another within each group (acutely infected patients, convalescent individuals, and vaccinated individuals). The results suggested protection against the B.1.1.7 variant by COVID-19 infection or vaccination.[64] However, resistance of B.1.1.7 and B.1.351 to CCP in neutralization assays was observed in another study.[65] CCP was obtained from 20 patients more than 1 month after SARS-CoV-2 infection. B.1.351 was more resistant to CCP than B.1.1.7.[65] Yet another study showed escape of a lineage of SARS-CoV-2501Y.V2 (also known as B.1.351) from neutralizing antibodies in CCP and also from three therapeutic monoclonal antibodies.[66] Hence, the evidence regarding using CCP for protection against emerging variants is scarce. B.1.617.2 was characterized as variant of concern by WHO on May 11, 2021. In one study, convalescent sera (collected from convalescent individuals prior to the emergence of variants, 32–57 days after symptoms onset) were of 3.2- to 4.9-fold lower neutralizing titer against the lentiviruses pseudotyped with spike proteins of B.1.351, B.1.617.2, AY.1, and C.37 variants, as compared to D614G spike protein. The sera of individuals vaccinated with mRNA-based and adenoviral vector-based vaccines had 2.5 to 4.0-fold lower neutralizing titers against the same variants, as compared to those sera against D614G spike protein.[67] Per data from National SARS-CoV-2 Strain Surveillance (NS3) program in October 2021, B.1.617.2 (Delta variant) was the predominant strain in the samples received for sequencing from public health agencies in the United States by the CDC.[68]

5 | UNCERTAINTY ABOUT THE FUTURE

Based upon the ongoing severity of the pandemic, available results of studies to date and paucity of alternative standard treatments, the use of high-titer CCP, as well as the evolving regulatory challenges, seem to continue. According to NIH donor center CCP collections, 44.3% units were high titer during collections from April 2020 to February 2021, with Ortho VITROS IgG S/C ratio of ≥9.5 for high-titer threshold.[69] Data from another collection center showed that only 19.5% CCP donations were high titer, per then EUA specified definition of a high-titer unit, in accordance with FDA EUA August 2020 issue.[70] Though currently downtrending, as data emerge from the clinical trials, the demand for high-titer units may increase, especially if CCP possibly is found efficacious for outpatient transfusions,[70] to modify disease progression.

Efficacy of CCP against the emerging SARS-CoV-2 variants is not known. Anti-SARS-CoV-2 antibodies target viral S-protein receptor binding domain (RBD), which binds to angiotensin converting enzyme 2 (ACE2) receptor.[71] Mutations leading to changes in RBD that may escape antibody protection have been mapped.[72] However, data about CCP use in patients infected with the variants are limited.[59,60,65] Like CCP, evidence about the efficacy of monoclonal antibodies treatment against the newly emerging variants is evolving. Neutralization assays using spike-pseudotyped lentiviral particles showed the Regeneron antibody cocktail (REGN10933 and REGN10987) escape by one such mutation (E406W).[72] Efficacy of vaccines against the different variants remains to be established.

The year 2020 started with a global outbreak of an unseen health crisis that changed the dynamics and focus of global healthcare. Among the preventive and therapeutic modalities, CCP was considered a key option, and blood establishments faced continuous, unprecedented challenges. As the pandemic continues to evolve, specifically with respect to increasing transmissibility and increasing variants, the regulatory aspects of collection

and therapeutic guidelines for CCP will continue to adapt.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

DISCLAIMER

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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