AABB Hot Topic Discussion: New Evidence Supporting COVID-19 Convalescent Plasma as An Effective Alternative Treatment Option with Immunosuppressed Patients
June 30, 2022

RESPONSES TO UNANSWERED AUDIENCE QUESTIONS

1. **Question:** Do you think that duration of COVID-19 convalescent plasma (CCP) treatment should be response-driven (i.e., viral load-driven)? We had complete responses after 5-6 units. What is the rationale for discontinuing after 1-2 CCP units if seeing a decline in viral load?
   Panel Response: The duration of treatment can absolutely be longer, though clinically and operationally (especially in an outpatient setting), giving two units typically works best. There is ample data showing that more CCP may be necessary to clear virus in patients with chronic or longstanding viral shedding. In addition, FDA's **Fact Sheet for Health Care Providers** addresses dosage and administration on page 2.

2. **Question:** Should donor plasma be ABO-matched to the recipient? Is it a mistake to assume group AB plasma is universal?
   Panel Response: AB plasma is the universal plasma, but is in limited supply (only 4% of donor are AB). It is best to use ABO-matched plasma, but most blood centers have policies on the amount of ABO-incompatible plasma that can be used (mostly because of shortages of ABO-compatible platelets) and that policy can be applied to CCP.

3. **Question:** How many units of CCP are needed for effective treatment, and are the coagulation factors in the plasma a consideration (i.e., over-coagulating a patient)?
   Panel Response: See response to question 1 on the number of units of CCP for treatment. Plasma does contain coagulant factors, but it also contains the natural anticoagulant factors, Protein C, Protein S and Antithrombin III which counterbalance the coagulant factors.
   In addition, FDA's **Fact Sheet for Health Care Providers** addresses dosage and administration on page 2.

4. **Question:** Due to the potential advantage of "hybrid plasma" (from vaccinated and recently recovered donors), do you recommend blood centers focus collection efforts on primarily these donors?
   Panel Response: Current FDA requirements in the **January 2022 CCP Guidance** **permit CCP collections from a "hybrid donor"** *under some circumstances*… as described under III.B.1.d.i.2. below (and as shown The **AABB Toolkit includes a flowchart (on page 3)** mapping FDA's current pathway for qualifying vaccinated and unvaccinated donors).
   - FDA requires that the **vaccinated donor have a positive diagnostic test AND symptoms as evidence of infection.**
   - **Current recommendations under III.B.d.i.2. state:**

     d. To ensure that COVID-19 convalescent plasma collected from donors contains antibodies directly related to their immune responses to SARS-CoV-2 infection, **you should not collect COVID-19 convalescent plasma from:**

i. Individuals who have received an investigational COVID-19 vaccine as a participant in a clinical trial, or received an authorized or licensed COVID-19 vaccine, **unless they:**

1) had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA (i.e., **individuals who meet the qualification for evidence of COVID-19 described in section III.B.1.a.1** of this guidance), AND

2) are within 6 months after complete resolution of COVID-19 symptoms.

5. **Question:** Can panelists comment on the use of Evusheld monoclonal Ab?
   Panel Response: For now, Evusheld is likely to be effective against the most common circulating variants. It is the only pre-exposure prophylaxis available for people who do not generate a good response to vaccines. For this reason, I recommend it to immunocompromised people and especially those with an inability to form strong antibodies after vaccination.

6. **Question:** The panel represents physicians and individuals from elite organizations in the North, have you considered regional (south, Midwest, etc.) physician and blood center champions?
   Panel Response: CCP needs champions everywhere. In fact, Dr. Joyner (who was unable to attend), Dr Grossman and Dr. Henderson are in the Midwest. CCP use and advocacy within one's own healthcare system and community is what is needed to ensure access to therapy and increase its use in eligible patients.
   - AABB's Plasma Antibody Network (PLAN) holds regular meetings making it possible to stay connected with CCP Champions in every area – refer to PLAN slide in the presentation by Ms. Carayiannis.
   - **The PLAN webpage currently lists the following resources:**

   Resources – watch for updates on emerging information:
   Clinical Practice Guidelines from the Association for the Advancement of Blood and Biotherapies (AABB): COVID-19 Convalescent Plasma
   National COVID-19 Convalescent Plasma Project

7. **Question:** Can you comment on the risk of transfusing antibody-dependent enhancing Abs with CCP collected from convalescent patients or vaccinated and infected patients?
   Panel Response: There is no current evidence that transfusion of CCP leads to antibody dependent enhancement.

8. **Question:** Blood centers are struggling with staffing and donor shortages. Are blood centers supported to ramp up their CCP collections?
   Panel Response: Blood centers are facing unprecedented challenges. In the beginning, CCP was collected by apheresis, which was extremely laborious since it was a completely different pathway from routine whole blood donations. Much of the CCP collected today is being collected during routine whole blood donations with only additional questioning and antibody testing added to the process.

9. **Question:** Based on the largely vaccinated population today, can we assume FFP has anti-COVID antibodies?
   Panel Response: Yes. FDA has often clarified that antibodies in FFP as a result of vaccination are not the equivalent of high-titer antibodies resulting from infection. The emergency use of CCP requires collections from donors who meet all eligibility requirements in FDA's Jan 2022 Guidance and are labeled as CCP based on testing specified in the EUA to confirm the presence of high-titer antibodies which are necessary for effective treatment of COVID-19. **Here are the regulatory details for your reference:**

(1) **FDA recommendations under III.B.1.a on page 7 of the Jan 2022 Guidance,** Investigational COVID-19 Convalescent Plasma | FDA require evidence of prior COVID-19 infection prior to donation.
(2) **FDA has just confirmed that the following FDA approved home tests can be used** as diagnostic evidence of COVID-19 infection to qualify CCP donors:

> **From:** CBER OBRR BPB Inquiries <CBEROBRRBPBInquiries@fda.hhs.gov>
> **Sent:** Wednesday, July 6, 2022 10:38 AM
>
> FDA has authorized several home tests to diagnose COVID- 19 (https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/in-vitro-diagnostics-euas-antigen-diagnostic-tests-sars-cov-2). Consequently, these authorized home tests are acceptable to meet the recommendations for donor qualification in the CCP guidance.
>
> The method for documenting the results of the home tests for COVID-19 may be determined by your facility.

(3) FDA recommendations require **additional titer testing post collection** as a manufacturing step in III.B.2, page 8 of the Jan 2022 guidance, using tests listed in **Appendix A on page 9 of the EUA at this link: https://www.fda.gov/media/141477/download**
(4) The AABB Toolkit includes a flowchart (on page 3) mapping FDA's current pathway for qualifying vaccinated and unvaccinated donors.

10. **Question:** LMIC do not have neutralizing titer kits available. Is there any research correlating it with od values?
Panel Response: High titer CCP is vetted on spike protein antibody measurement platforms, not by neutralization. The FDA authorized platforms for measurement have been correlated with neutralization activity. Therefore, high titer CCP contains an amount of antibody that is considered to have a high level of neutralizing activity.
The EUA and FDA's recommendations require additional titer testing post collection as a manufacturing step in III.B.2, page 8 of the Jan 2022 guidance, using tests listed in **Appendix A on page 9 of the EUA at this link: https://www.fda.gov/media/141477/download.**

Note that the "qualifying result" or "cut-off" varies by test as necessary for correlation:

Appendix A: Table of Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies

Tests Acceptable for Use in the Manufacture of COVID-19 Convalescent Plasma with High Titers of Anti-SARS-CoV-2 Antibodies			
Manufacturer (listed alphabetically)	**Assay**	**Qualifying Result**	**Date of Listing under this EUA**
Abbott	AdviseDx SARSCoV-2 IgG II (ARCHITECT and Alinity i)	≥ 1280 AU/mL	December 28, 2021
Diasorin	LIAISON SARS-CoV-2 TrimericS IgG	≥ 87 AU/mL	December 28, 2021

EUROIMMUN	Anti-SARS-CoV-2 S1 Curve ELISA (IgG)	>55 RU/mL	February 9, 2022
GenScript	cPass SARS-CoV-2 Neutralization Antibody Detection Kit	Inhibition ≥ 80%	December 28, 2021
Kantaro	COVID-SeroKlir, Kantaro Semi-Quantitative SARS-CoV-2 IgG Antibody Kit	Spike ELISA > 69 AU/mL	December 28, 2021
Ortho	VITROS Anti-SARS-CoV-2 IgG Quantitative Reagent Pack	>200 BAU/mL	December 28, 2021
Roche	Elecsys Anti-SARS-CoV-2 S	> 210 U/mL	Dec 28, 2021

11. **Question:** Ab typically disappears sometimes within 3 months. Are blood centers testing for titers to make sure CCP is going to be effective?
Panel Response: Yes, as described in the response to question 10. Before a collection can be labeled as CCP, the EUA and FDA guidance require CCP collections to be tested to confirm the presences of high titer of antibodies using an FDA approved test (titer is specific for each test specified in Appendix A above). Also, note that FDA's January 2022 CCP Guidance recommendations under III.B.1.d.i.2 are intended to ensure antibodies are a result of recent infection:

> d. To ensure that COVID-19 convalescent plasma collected from donors contains antibodies directly related to their immune responses to SARS-CoV-2 infection, you should not collect COVID-19 convalescent plasma from:
> i. Individuals who have received an investigational COVID-19 vaccine as a participant in a clinical trial, or received an authorized or licensed COVID-19 vaccine, unless they:
>
> 1) had symptoms of COVID-19 and a positive test result from a diagnostic test approved, cleared, or authorized by FDA (i.e., individuals who meet the qualification for evidence of COVID-19 described in section III.B.1.a.1 of this guidance), AND
>
> 2) are within 6 months after complete resolution of COVID-19 symptoms.